MASTER OF PHILOSOPHY

Quality of Life Assessment in Patients Undergoing Laparoscopic Cholecystectomy

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Quality of Life Assessment in Patients Undergoing Laparoscopic Cholecystectomy

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Declaration

I declare that the research described in this thesis is entirely my own work and was carried out in the Department of Surgery, The Queen's University of Belfast, between September 2000 and April 2005. It has not been submitted to any other institution.

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Dedication

To Julie, for her unconditional support, understanding, and the sacrifices made to help complete this thesis, and to Joel and Jorja for the time I wish I could have spent with them.

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Publications and Presentations

Presentations

1. **G R Kirk**, J Clarke, M Regan, T Diamond, W D B Clements. Predicting gastrointestinal quality of life in patients following laparoscopic cholecystectomy. *Surgical Trainees Prize Day, Northern Ireland, November 2004.*

2. **G R Kirk**, J Clarke, L McKie, T Diamond, W D B Clements. High Manning Scores – A positive predictor of poor outcome following laparoscopic cholecystectomy. *Ulster Society of Gastroenterology, Belfast, February 2005.*

3. **G R Kirk**, J Clarke, M Regan, L KcKie, T Diamond, W D B Clements. Does irritable bowel syndrome affect quality of life in patients following laparoscopic cholecystectomy ? *Association of Surgeons of Great Britain and Ireland, Oral presentation for 6 of the best endoscopic papers, Glasgow, April 2005.*

4. **G R Kirk**, J Clarke, L McKie, T Diamond, W D B Clements. High Manning Scores – A positive predictor of poor outcome following laparoscopic cholecystectomy. *European Association of Endoscopic Surgery, Venice, June 2005.*

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1. **G R Kirk**, J Clarke, M Regan, T Diamond, W D B Clements. Does irritable bowel syndrome affect quality of life in patients following laparoscopic cholecystectomy? *British Journal of Surgery* 2005; 92(Supp 1):158

2. **G R Kirk**, J Clarke, M Regan, T Diamond, W D B Clements. Predicting gastrointestinal quality of life in patients following laparoscopic cholecystectomy. *Ulster Medical Journal 2005; In press.*

3. **G R Kirk**, J Clarke, L McKie, T Diamond, W D B Clements. High Manning Scores – A positive predictor of poor outcome following laparoscopic cholecystectomy. *Surgical Endoscopy 2005; In press.*

Abbreviations

ASA	American Society of Anaesthesiologists
BABS	Bradburn Affect Balance Scale
BP	Blood Pressure
CBD	Common Bile Duct
EORTC	European Organization for Research and Treatment of Cancer
ESWL	Extracorporeal Shock Wave Lithotripsy
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-G	Functional Assessment of Cancer Therapy (General)
FD	Functional Dyspepsia
FDDQL	Quality of Life Questionnaire for Functional Digestive Disorders
FGID	Functional Gastrointestinal Disorders
GI	Gastrointestinal
GIC	Gallstone Impact Checklist
GIQLI	Gastrointestinal Quality of Life Index
GSRS	Gastrointestinal Rating Scale
HRQOL	Health Related Quality of Life
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IBS-QOL	Irritable Bowel Syndrome – Quality of Life
MICOL	Multicentre Italian Study of Cholelithiasis
NHP	Nottingham Health Profile
OBDI	Owestry Back-Disability Index
PGWB	Psychological General Well Being Index
PROQOLID	The Patient Reported Outcome and QOL Instruments Database
Q1	Abbreviation for Questionnaire Taken at 0 Weeks
Q2	Abbreviation for Questionnaire Taken at 6 Weeks
Q3	Abbreviation for Questionnaire Taken at 3 Months
Q4	Abbreviation for Questionnaire Taken at 2 Years
QOL	Quality of Life
SCL-90-R	Hopkins Symptom Checklist
SIP	Sickness Impact Profile
SF-24	MOS 24-Item Short-Form Health Survey
SF-36	MOS 36-Item Short-Form Health Survey
SOD	Sphincter of Oddi Dysfunction
SQLI	Spitzer Quality of Life Index
TIME	Toolkit of Instruments to Measure End-of-Life Care
USS	Ultrasound Scan
VAS	Visual Analogue Scale
WHO	World Health Organisation

Ethical Approval

All studies were carried out following approval from the Ethics Committee, Department of Health and Social Services, Northern Ireland.

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Introduction

Philipe Mouret performed the first laparoscopic cholecystectomy in 1987, and since then it has become the 'gold standard' treatment for symptomatic gallstones. It had undoubted benefits over the conventional open procedure, such as reduced morbidity and mortality, a shorter hospital stay and quicker return to normal daily activities. This improved risk to benefit ratio has seen an increasing number of cholecystectomies performed, without a parallel increase in the prevalence of gallstones. This could represent a higher patient demand for 'key hole' surgery, or a reduced threshold for intervention, with surgery being performed for poorly defined indications such as functional gastrointestinal disorders.

Independent of the operative technique, there is a significant proportion of patients who complain of persistent symptoms after cholecystectomy, a condition described as postcholecystectomy syndrome. There is evidence to show that patients who experience a predominance of functional symptoms such as altered bowel habit and those requiring psychotropic medications have a higher rate of persistent symptoms following surgery.

Irritable bowel syndrome is a functional colonic disorder characterised by abdominal discomfort, along with altered defaecation or change in bowel habit. Many of the symptoms of IBS overlap with those of functional dyspepsia or gallstones, and a higher rate of anxiety and depression has been observed in this group. As yet there is no study to show that patients with irritable bowel syndrome and gallstones have a worse outcome after cholecystectomy, but population based studies have shown that they do have a higher rate of cholecystectomy when compared with the general

population. A significant proportion of these patients may be having cholecystectomies for symptoms of colonic rather than biliary origin. If we could predict patients who were less likely to benefit from surgery, and treat them expectantly, there would be financial gains and benefits in terms of patients' health from reduced morbidity by unnecessary surgery.

Quality of life assessment is a measurement tool that researchers can use to investigate outcome after an intervention or treatment. Methods of assessing quality of life and its clinical application have gained popularity and improved significantly over the last decade. In this study, quality of life measurement is the principle means used to examine what effect irritable bowel syndrome has on outcome after laparoscopic cholecystectomy.

Section 1

QUALITY OF LIFE AND GALLSTONES

The physicist Lord Kelvin (1824-1907)

"When you can measure what you are speaking of and express it in terms of numbers you know something about it: when you cannot express it in terms of numbers your knowledge is of a meagre kind"

Chapter 1

Quality of Life Measurement

1.1 Introduction

In an era when evidence based medicine and revalidation are at the forefront of clinical practice and where governments, the public and indeed the media are becoming increasingly critical of how patients are treated, it has become essential to provide evidence for the benefits of surgical intervention. Traditionally, outcome measurements in surgery have focused on Figures such as morbidity rates, disease free periods, length of hospital stay, recurrence rates and of course, mortality (O'Boyle, 1992; Fraser, 1993). Quality of life (QOL) is an alternative and valuable tool which researchers can use to measure outcome after surgery. In terms of medicine, it allows objective measurement of the effects an illness or treatment can have on a patient's daily life and life satisfaction; that is, it can be used to evaluate human and financial costs. Its assessment in the medical arena has dramatically increased in popularity over the last decade. This trend has been observed in the surgical literature. In 1992 a Scottish group simply looked at the number of QOL studies in surgery cited on Medline. They found an exponential rise in published articles over the previous two decades. Their Figures ranged from 92 cited between 1975 and 1977, to over 2 thousand cited between 1996 and 1998 (Camilleri-Brennan and Steele, 1999). As we shall discuss, QOL is more often mentioned than measured accurately (Wood-Dauphinee, 1996).

1.2 Quality of life – the concept

Quality of life is not a new concept; it was first defined by the World Health Organisation (WHO) in 1948 as not only the absence of disease and infirmity , but also the presence of physical, mental and social wellbeing (Constitution of the World Health Organisation, 1952). This definition is not all encompassing and by no means has universal acceptance (O'Boyle, 1992; Olschewski *et al.*, 1994; Camilleri-Brennan and Steele, 1999). More recently, the WHO quality of life group have expanded this further to incorporate how an individual's cultural and social value system and their goals and expectations may influence global QOL (World Health Organisation Quality of Life Group, 1996).

In terms of medicine, health related quality of life (HRQOL) aims to objectively quantify these factors by measuring subjective attitudes and experiences of physical, social and emotional health (Guyatt *et al.*, 1993; Testa and Simonson, 1996). Estimating a patient's perspective of their own health status acts as a powerful tool to assess and explain disease outcome. For this reason QOL measurements are often the endpoint of clinical trials and outside the medical arena can incorporate non-health related elements, such as personal finances, leisure time and housing issues (Langenhoff *et al.*, 2001). Potential application of obtained results include identification of problems with individual patients or within populations, evaluation of treatment efficacy, implementation of policy, assessment of quality of health care, economic evaluation and improvement of disease knowledge (Fitzpatrick *et al.*, 1992; Borgaonkar and Irvine, 2000)

Whatever the definition, it is largely agreed that QOL is a complex multidimensional concept made up from three principle domains: physical, psychological and social (O'Boyle, 1992; Fitzpatrick *et al.*, 1992; Olschewski *et al.*, 1994; Testa and Simonson, 1996). The physical domain measures how illness affects a patient's perception of his or her own bodily function. The psychological domain includes aspects of a patient's emotional and mental wellbeing such as mood, anxiety, concerns, fear and anger. Finally, the social domain refers to how a patient interacts with and is incorporated into their social role, for example relationship with family, integration into the workplace and spiritual aspects. Each of these domains can be measured in two dimensions: objective assessments of function or health (the Y axis in Figure 1) and more subjective perception of health (the X axis). The patient's subjective perception translates the objective assessment into the actual QOL experienced (or Q in Figure 1). In other words, the global quality of life score or value takes into account the subjective perception and objective measurements of each of these items (Bergner, 1989; Testa and Simonson, 1996). Subjective perceptions of health vary greatly between individuals and are influenced by many factors such as previous experience, family support, and financial security. Two people with exactly the same health profile may have very different qualities of life. For example one individual with Crohn's disease may hold down full-time employment, have an active family and social lifestyle, while another patient with the same disease extent and severity may be depressed, unemployed and unable to fulfil their role in the home environment.

Every domain can be further subdivided into different components, for example symptoms, ability to function and disability, within the physical domain. These components can be measured in isolation or collectively. Many of these components cannot be observed directly; they are typically evaluated according to the principles of item-measurement theory (Lord, 1980). This theory proposes that there is a single true QOL value, Q, that cannot be measured directly, but that can be measured indirectly by asking a series of questions called 'items' . In Figure 1, Z represents this observed or measured value. If the items have been chosen properly, the resulting scale of measurement, Z, should differ from the true value, Q, only by random error of measurement.

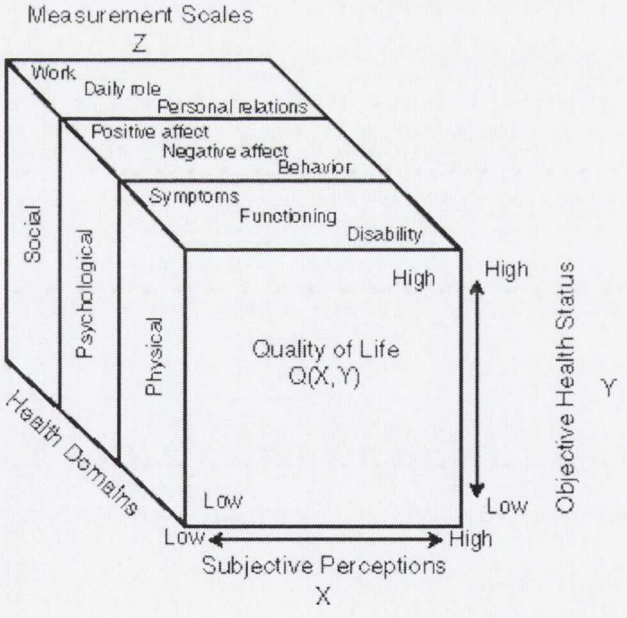


Figure 1. Conceptual scheme of the domains and variables involved in a quality of life assessment.

The x axis represents subjective perceptions of health, the y axis objective health status, the coordinates Q(X,Y) the actual quality of life, and Z the measurement of the actual quality of life associated with a specific component (e.g. positive affect) or domain (e.g. the psychological domain).

QOL is also dynamic (Bergner, 1989; Olschewski *et al.*, 1994), that is it varies with respect to time. It can change from day to day or even from hour to hour and for this reason it is best to measure changes in quality of life over time. This is particularly useful when evaluating the effects of treatment on disease. Assessments can be made before, and at regular intervals during and after, treatment to gauge treatment efficacy, disease regression or recurrence.

1.3 Measuring quality of life

Quality of life measurements usually take the form of a structured questionnaire commonly known as an instrument, which has been specially designed to assess each of the three domains. The patient's answers are scored, allowing qualitative information to be converted to quantitative data (Guyatt *et al.*, 1993; Camilleri-Brennan and Steele, 1999). Each domain can be scored separately or globally, giving a single quality of life index. Variation between instruments usually relates to how questions are formatted, how much and to what extent they emphasise each domain and to the degree of subjectivity involved.

1.3.1 Types of Instruments

There are three main types of instrument available (Moyer and Fendrick, 1998; Borgaonkar and Irvine, 2000), the global , the generic and the disease or symptom specific . An example of a global instrument would be a visual analogue scale. This is a graded scale from 1 to 10, and used most frequently in clinical practice to assess pain. They themselves are simple and quick to administer, giving an instant value that can be correlated with previous results or used and then applied at that

single point in time to assess the measured variable. The data gathered from these instruments is however of limited value when detailed quality of life assessment is needed (Testa and Simonson, 1996; Irvine, 1997; Borgaonkar and Irvine, 2000). A question such as "Please mark on this scale your current quality of life" would give Figures much too vague and imprecise to be interpreted exactly. For this reason clinicians and researches favour more detailed instruments that assess each domain separately.

Generic instruments are commonly used in clinical research. They are designed for application across a diverse spectrum of patients or disease populations (Bergner *et al.*, 1981; Ware, Jr. and Sherbourne, 1992), and are frequently used when a general survey of health is needed. They cover quality of life in a broad sense and are particularly useful where comparison between disease groups or populations is needed (Kaplan *et al.*, 1989; Testa and Simonson, 1996; Camilleri-Brennan and Steele, 1999; Langenhoff *et al.*, 2001). Until recently this type of instrument has been the predominant method for HRQOL assessment. Examples of generic instruments include the Short Form 36 (SF-36) (Ware, Jr. and Sherbourne, 1992), the Sickness Impact profile (SIP) (Bergner *et al.*, 1981) and the Nottingham Health Profile (NHP) (Hunt *et al.*, 1981). Despite being the best type of instrument for detecting unexpected disease impact, and for population comparison they do lack sensitivity and can fail to quantify or even identify clinically significant changes brought about by the disease being studied (Guyatt *et al.*, 1993; Testa and Simonson, 1996; Borgaonkar and Irvine, 2000).

As the names suggests, disease or symptom specific questionnaires are tailored for patients with a particular disease or symptom. They focus on domains most relevant to the disease under study, and on the characteristics of patients in whom the disease is most prevalent (Testa and Simonson, 1996). Rather than a global health assessment they can give important information on specific areas of quality of life. They are particularly good when used in clinical trials to evaluate treatment efficacies (Guyatt *et al.*, 1987; Guyatt *et al.*, 1989). Overall they tend to be more sensitive to small changes in quality of life (Guyatt *et al.*, 1993; Borgaonkar and Irvine, 2000), but can sometimes overlook unexpected effects. For this reason it is now becoming more common to combine both generic and disease specific instruments in clinical trials. Examples of disease specific questionnaires include "The Gastrointestinal Quality of life Index" (GIQLI) (Eypasch *et al.*, 1995), the IBS-QOL (Patrick *et al.*, 1998) and, possibly the most widely used instrument in cancer research, the EORTC QLQ-C30 (Fitzsimmons *et al.*, 1999). The latter was designed by the European Organization for Research and Treatment of Cancer (EORTC). It uses a modular approach, with a core questionnaire consisting of 30 questions (EORTC QLQ-C30) and then additional questionnaires to focus more closely on specific types of cancer e.g. QLQ-PAN26 dealing with pancreatic cancer (Bassi *et al.*, 1999), QLQ-CR38 for colorectal cancer (Sprangers *et al.*, 1999) and the QLQ-LC13 used in lung cancer (Bergman *et al.*, 1994). There are literally hundreds of disease specific and symptom specific questionnaires available (Berzon *et al.*, 1995). However, many common diseases still have no validated instrument and for this reason, if inappropriate questionnaires are used, unanticipated events can be easily missed.

1.3.2 Measurement properties of QOL instruments

Very definite measurement properties exist for quality of life instruments; they assist in the development of new instruments and ensure that they measure what they purport to measure both accurately and reliably. The key concepts include validity, reliability and responsiveness (Fletcher *et al.*, 1992; Muldoon *et al.*, 1998; Cohen, 1999) . A clear understanding of these principles is required if development of a new HRQOL questionnaire is to be successful (Brown, Jr., 1999) and be accepted by investigators.

Validity is probably the single most important property used. It aims to show that the instrument measures what it intends to measure and not some other factor, thus proving that it can be used appropriately for a particular disease or clinical situation. Referring back to Figure 1, validity should show that Z correctly measures Q. There are three main types of validity which are quoted in HRQOL validation papers. In brief, content validity asks whether the instrument samples the domain adequately and to what extent the questions comprehensively cover the population, disease or symptomatic state. Criterion validity compares how the new instrument correlates with what is commonly accepted as being the gold standard. So at sometime during the validation process both the new and the gold standard instruments are administered concurrently and the results correlated. If results correlate then it can be accepted that the new instrument is a valid measure of the disease in question. Finally, construct validity uses an approach whereby the instrument is tested against a hypothesis. For example, if it is predicted that a person with Crohn's disease has poorer social functioning with increased disease severity, and low scores are measured with the new instrument in this domain, then validation

is strengthened. When new instruments are being published, details of the validation process should be clearly stated, with reference to other previously validated instruments, if available. A good example of the validation process is seen in the development of the GIQLI (Eypasch *et al.*, 1995; Quintana *et al.*, 2001). The authors showed evidence of good criterion validity when data was correlated with the Spitzer Quality of Life Index (SQLI) (Spitzer *et al.*, 1981) and the Bradburn Affect Balance Scale (BABS) (Bradburn and Noll, 1969). They also proved construct validity in patients with gastrointestinal disease when looking at disease severity.

Reliability or reproducibility can be demonstrated if the questionnaire gives consistent results when repeatedly administered to the same individual or stable group of patients whose disease state has not changed with time. Again the GIQLI showed this when repeat testing of 25 patients after 48 hours gave similar results. There are three types of reliability measurement (Fletcher *et al.*, 1992; Guyatt *et al.*, 1993). Firstly, test re-test reliability which we have already mentioned. Secondly, internal consistency reliability that determines the extent to which a group of questions are measuring a particular domain and finally, inter-rater reliability which looks at the effects of instrument administration by different interviewers.

Responsiveness measures how well a questionnaire detects small changes in patient status; that is, the magnitude of change in the HRQOL score should reflect a similar change in the patient's clinical state. In Figure 1 therefore, the responsiveness is a measure of the association between change in the observed score Z, and the change in the true score, Q. The GIQLI measured responsiveness on patients undergoing laparoscopic cholecystectomy (Quintana *et al.*, 2001), and showed

improvement of scores as the patients' clinical status slowly improved post-operatively. Responsiveness is particularly important when any instrument is used in a longitudinal study (Camilleri-Brennan and Steele, 1999).

1.3.3 Instrument selection

Choosing an appropriate questionnaire is an important first step, if statistically significant results are to be obtained. The choice of instrument depends largely on what type of study is being performed. Clinical trials which look at outcomes of treatment over time (e.g. drug trials) are more responsive to a disease specific questionnaire. The disease specific questionnaires are usually developed so as to detect subtle disease and treatment related effects, which reflect issues of importance to the patient. Generic instruments tend to focus on broad aspects of QOL and health status, and are intended for use in general populations across a wide range of disease conditions. For this reason they are better suited to cross sectional studies (Camilleri-Brennan and Steele, 1999). Many modern questionnaires use a modular approach, for example the EORTC QLQ-C30 (Fitzsimmons *et al.*, 1999) and the Functional Assessment of Cancer Therapy (FACT - G) (Lee *et al.*, 2004a). These generic questionnaires make up the core of questions, but have add-on disease specific components. This has the advantage of combining both generic and disease specific properties into one index.

For many disease states however, a specific questionnaire is not available and the most closely related instrument should be chosen. In some circumstances, a non-validated instrument may be available; and in these cases it is good practice to use an already validated questionnaire in parallel (Fletcher *et al.*, 1992).

There are several resources available to help individuals find the most appropriate instrument(s) for their study. The best place to start is probably a journal search using Medline or a similar available search method. Over the last decade there has been an exponential increase in the number of publications relating to quality of life. In this context the most useful are probably review articles looking at already validated instruments in various specialist fields, for example in cancer surgery (Langenhoff *et al.*, 2001), gastroenterology (Borgaonkar and Irvine, 2000) or in palliative care (McMillan, 1996). These types of papers give the reader an overview of what disease specific instruments are available in their area of interest. Yacavone *et al* recently published a review article in the American Journal of Gastroenterology, which discussed the most up to date generic and disease specific questionnaires available in their field (Yacavone *et al.*, 2001).

There have been five publications of the 'quality of life bibliography and indexes' (Spilker *et al.*, 1990; Berzon *et al.*, 1995). This is an extremely useful source of information on QOL instruments but, unfortunately, it has not been updated since 1994. Several detailed reviews on the methods for evaluating and selecting HRQOL instruments have been published. One by Shuvayu *et al* (Shuvayu *et al.*, 1999) is of particular value. They used the selection of an asthma specific questionnaire as an example in their paper.

The internet is another valuable resource to aid instrument selection. Apart from generic search engines such as Yahoo, Altavista and Google, dedicated HRQOL websites exist with instrument lists and descriptions. Some sites have search facilities to help selection.

The Quality of Life Instruments Database (http://www.proqolid.org/) is probably the most comprehensive and user friendly online database available. The project was initiated by the Mapi Research Trust in Lyon, France. Initially called QOLID (Quality of Life Instruments Database), the project's purpose was to provide all those involved in health care evaluation with a comprehensive and unique source of information on HRQOL measures available through the internet. PROQOLID lists over 1000 questionnaires giving detailed information, including contact information and references on over 470. It has two types of membership; the first is free and includes access to information such as the objective of development, name of the author, type of instrument, mode of administration, target population, original language and the list of available translations.

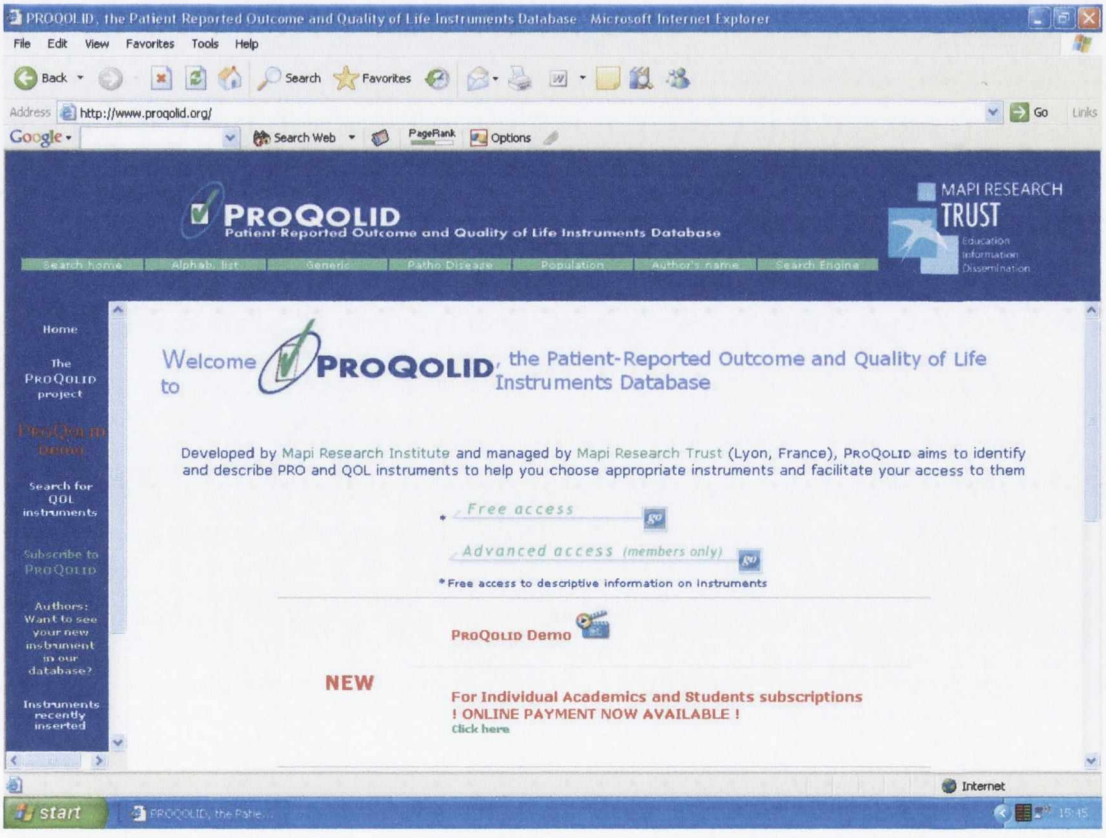


Figure 2 The Patient Reported Outcome and QOL Instruments Database (PROQOLID)

The second section requires a subscription fee and includes full references, copyright and detailed contact information as well as copies of over 170 original questionnaires, 100 translations and over 50 user manuals. PROQOLID is updated in close collaboration with the instruments' authors on a regular basis. Fifty or more new instruments are added to the database annually. The home page for the website is shown in Figure 2 above.

Several websites that focus on disease specific areas of medicine are available.

http://www.atsqol.org/ - American Thoracic Society

http://www.qoltech.co.uk/ - QOLTECH website

http://www.chcr.brown.edu/pcoc/toolkit.htm - TIME

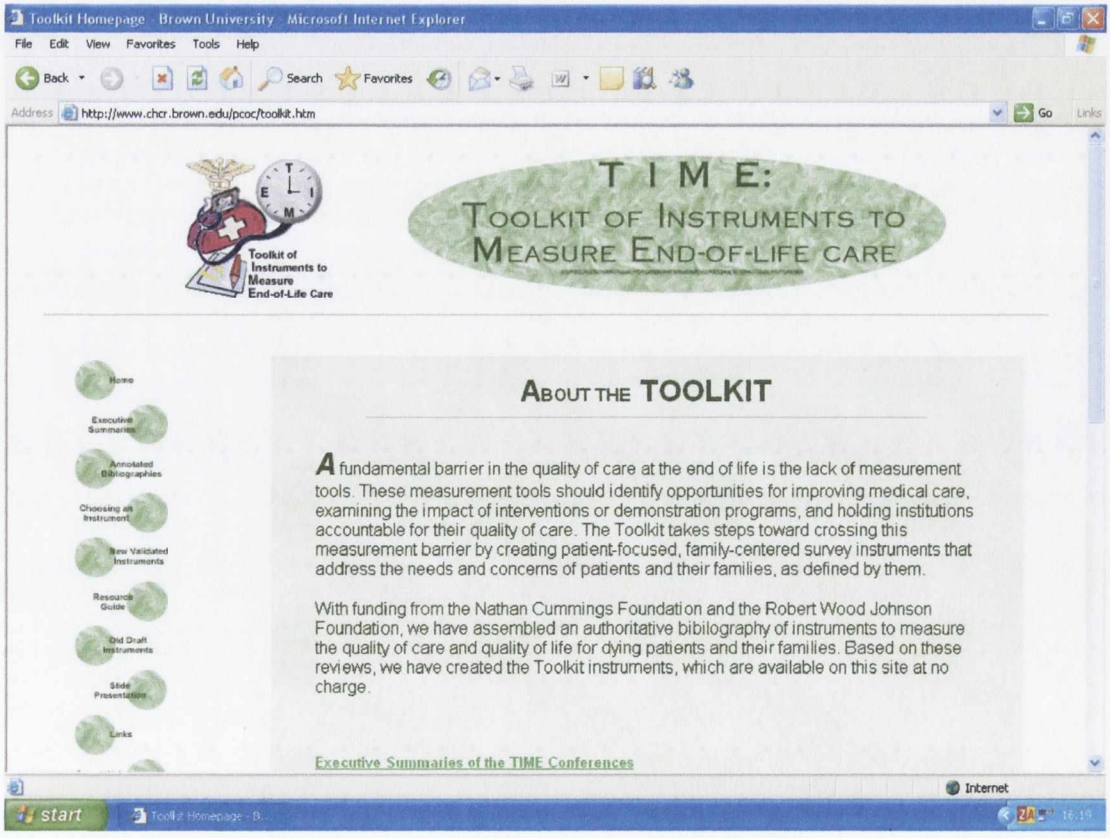


Figure 3 Toolkit of Instruments to Measure End-of-Life Care (TIME)

The American Thoracic Society webpage is designed for researchers who are interested in QOL measurement for patients with respiratory disease. They give detailed information on over 70 relevant questionnaires. What is also very useful is that they subdivide questionnaires in terms of disease states, for example asthma, cystic fibrosis and lung cancer. They give detailed and referenced reviews of which QOL instruments have been used and are most useful with each condition. The QOLTECH website is a similar, but smaller site, concentrating solely on asthma. The "Toolkits of Instruments to Measure End-of-Life Care" (TIME) website, focuses on QOL for the dying patient (Figure 3). It is an excellent resource for practitioners and care givers who need information on QOL in areas related to the terminal phase of life e.g. pain, emotional and cognitive symptoms and functional status.

Many of the more popular and widely validated questionnaires have their own websites.

http://www.eortc.be/ - EORTC webpage

http://www.sf36.com/ - SF36 webpage

http://www.facit.org/ - FACIT webpage

The Functional Assessment of Chronic Illness Therapy (FACIT) website (Figure 4) is particularly well designed and easy to navigate. This group published its first questionnaire in 1993 (Cella *et al.*, 1993), the FACT-G questionnaire which looked at QOL in cancer patients. Since then it has produced over 40 further instruments. It is one of the few generic questionnaires to work on a modular basis, but as well as cancer related instruments it now has questionnaires for other illnesses such as

multiple sclerosis and HIV. The website lists in detail the core and disease specific questionnaires that are available. It also provides a wide range of facilities, including access to validation papers, translations, scoring guidelines and database programs to help with interpretation.

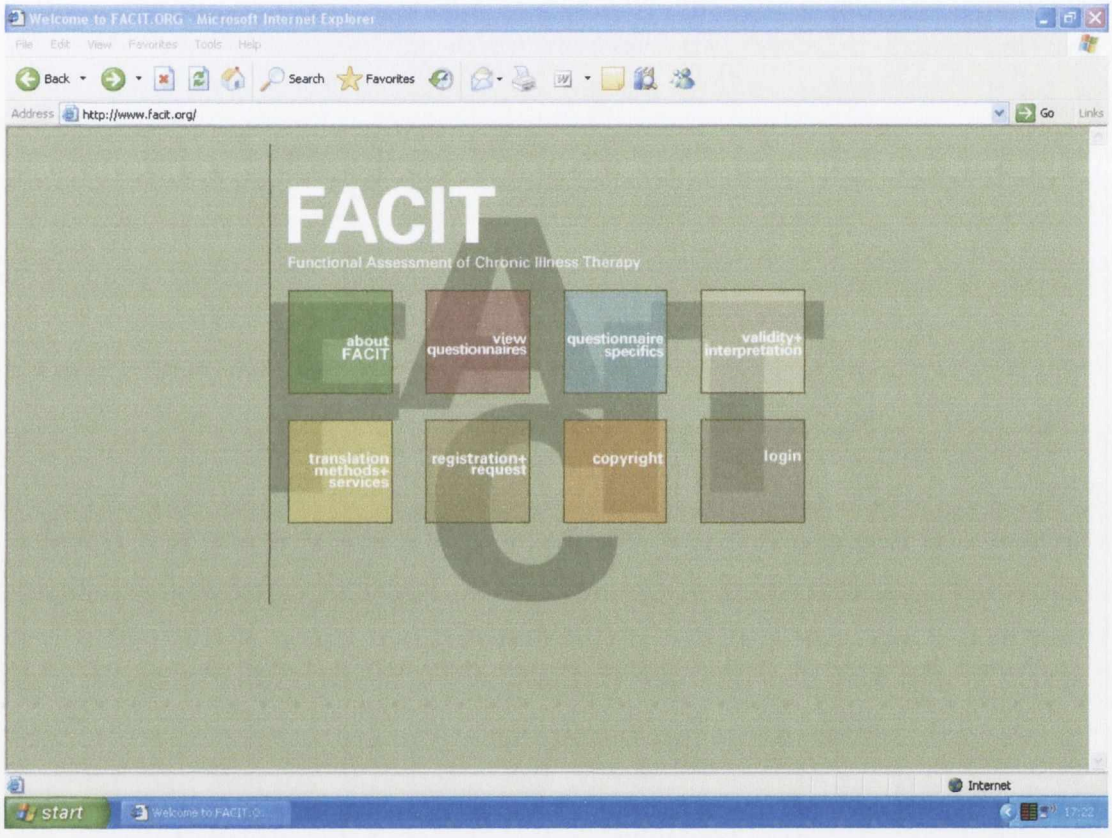


Figure 4 The Functional Assessment of Chronic Illness Therapy (FACIT)

Two journals devoted solely to QOL publications exist:

http://www.hqlo.com/home/

"Health and Quality of Life Outcomes" is a web-based only journal (Figure 5). It has on average, 5 to 10 new QOL papers published per month. Submission is online and peer reviewed. All accepted articles are referenced on PubMed.

http://www.kluweronline.com/ISSN/0962-9343/CONTENTS

"Quality of Life Research" is a subscription based journal, with monthly publication. Again articles are peer reviewed and referenced on Medline. It is currently on its 14th volume and has a wealth of resources spanning the last decade.

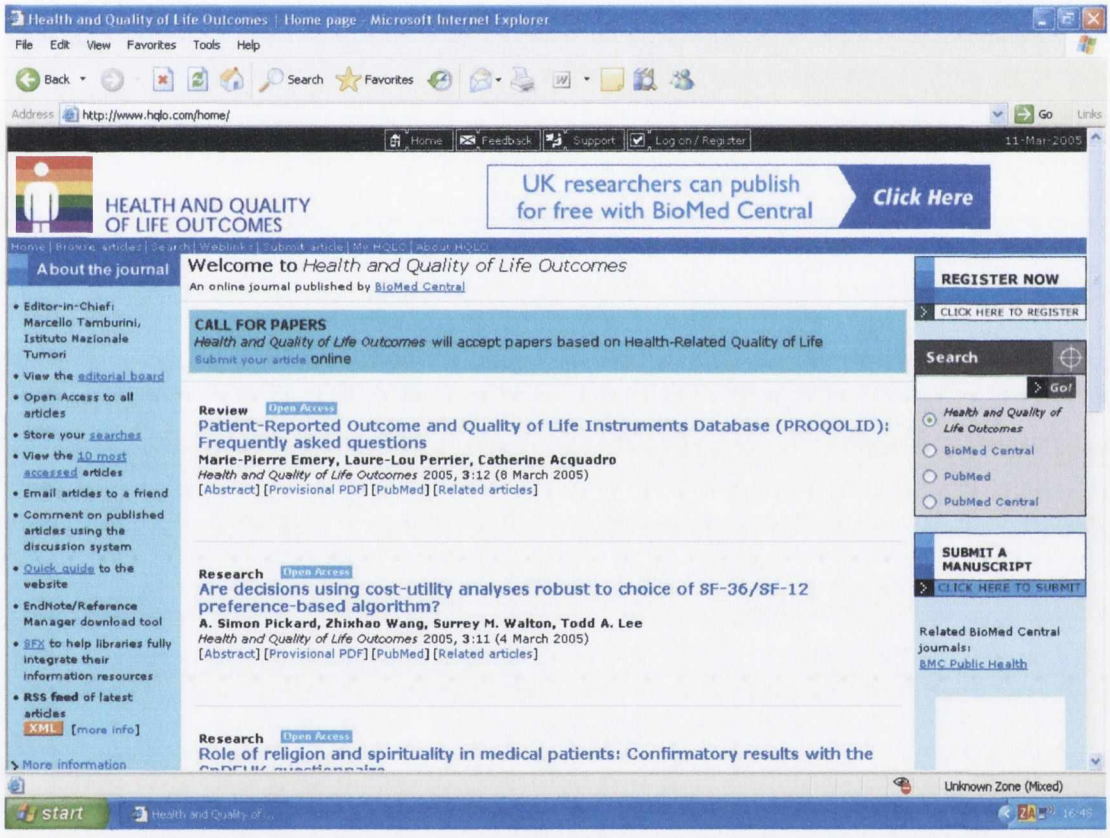
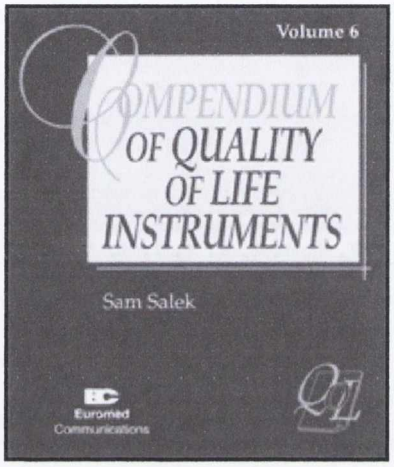


Figure 5 Health and Quality of Life Outcomes website

Finally, there are several books which extensively review generic and disease specific questionnaires (Bowling, 1995; Bowling, 1997). The Compendium of Quality of Life Instruments (Salek, 1998) can be found online at:



http://www.euromed.uk.com/qolcompendium.htm

There is a wealth of data and resources available to help researchers choose the most appropriate questionnaire for their study. Some of the basic principles that should be considered when selecting an instrument include:

- There should be documentation concerning the development and psychometric properties of the instrument and in particular, concerning its validation, reliability, sensitivity and responsiveness.
- There should be evidence that the instrument has been developed for and tested in a wide range of patients with the target disease states or receiving the intended treatment modalities.
- Instruments should be valid for use in patients with the relevant educational, cultural and ethnic backgrounds.

- If additional language versions are required, they should be developed and tested using formal procedures of forward and backward translation.
- If generic and disease specific questionnaires are to be combined they should be compatible.
- The feasibility of the study should be considered, for example length of the questionnaire, how long does it take to complete, how easily understood are the questions and are there any difficult or embarrassing questions?
- Are there reference data or interpretation guidelines available? These are important for analysis of results and design of the study (e.g. power calculation)

1.3.4 Administration of selected instrument

There are several ways that HRQOL instruments can be administered (i.e. self, interviewer, telephone and proxy). Most questionnaires are designed to make self administration straightforward. They are written in a language easily understood by patients, require only tick box answers and take less than 10 minutes to complete. All these factors are important to improve compliance and accurate data collection. There is however a greater risk of misinterpretation and blank questions when compared to an interviewer, which is recommended especially when there is a degree of cognitive impairment or illiteracy (Guyatt *et al.*, 1993; Camilleri-Brennan and Steele, 1999). There is however an argument that an interview technique does add a degree of external bias to the questioning, and patients may be reluctant to express their true feelings especially when faced with more intimate questions. Self administration is therefore widely accepted as being the gold standard method of instrument

administration. On rare occasions patients may not be physically or mentally capable of completing a questionnaire. In these circumstances a proxy respondent can be used, for example in patients with terminal illness a close relative who has first hand insight into the patient's everyday quality of life can be recruited (Guyatt *et al.*, 1993; Olschewski *et al.*, 1994). Care should be taken in data interpretation from proxy respondents; there is evidence both for and against their use. Some authors suggest very good correlation of responses between patients and close relatives, particularly for functional assessment (Sneeuw *et al.*, 1997; Sneeuw *et al.*, 1998), while others have shown significant observer induced bias, inter-observer variation and poor correlation in domain assessment other than the physical one (Blazeby *et al.*, 1995; Pierre *et al.*, 1998).

The timing of assessment is dependant on the type of disease and on study design. In general, a minimum of three assessments are advised, for example the first as a baseline before treatment is started, the second during the treatment period and third after treatment has finished. Many studies also assess long-term outcome with a further assessment some 6-12 months later. With increased frequency of questioning there is certainly a higher yield of quality of life data, but cost of implementation and complexity of both administration and of data analysis should be considered. Large numbers of questionnaires may also have a negative affect on patient compliance. Other characteristics to improve compliance include a self administered questionnaire taking less than 10 minutes to complete , containing less than 30 questions and being easy to understand (Fraser, 1993). The EORTC group published detailed guidelines for improving data quality and compliance in clinical trials in 1999 (Young and Maher, 1999).

1.4 Interpretation and clinical application

1.4.1 Introduction

We have described the principle of HRQOL measurement and given some information on data collection, but what of interpretation of these results? What is the clinical relevance of a particular QOL score and how important are the observed changes in patients' QOL? The scales and instruments used may be poorly understood by many clinicians (and patients), and they might reasonably ask how to interpret any QOL changes observed. A significant proportion of this comes down to simple familiarity with the scales used. Blood pressure (BP) measurement is one of the most widely used medical measurements. Both clinicians and patients are familiar with its use and understand its principle. The association between elevated BP and increased mortality is well recognised, and most clinicians would consider therapy if repeated diastolic BP exceeds 100 mmHg. There is however, much less familiarity with the scales used in QOL measurement. Hence, the need for information about the level of QOL that is to be expected for ill patients and guidelines to help decide what magnitude of change makes treatment worthwhile. No single approach is likely to provide a complete feel for the meaning of QOL measurements, and thus it is important to use a variety of methods for obtaining familiarity.

1.4.2 Examination of methods

One suggested method of scrutinizing a HRQOL article is to consider it in 3 distinct subheadings:

a. Have the investigators measured aspects of health that are important?

The ultimate aim of QOL assessment is to measure the effect treatment has on patients' lives. Having information on HRQOL helps clinicians make informed decisions about treatment they provide. In addition to changes in clinical and physiological variables, patients expect an improvement in how they feel or how long they live. With this in mind, clinicians need to be sure that the QOL research they are reading shows a valued effect in patient terms; that is, any measured change in QOL will have a significant bearing on how a patient feels or interacts with his or her physical and social surroundings. Investigators should show this in their work. They may do this by describing in detail the questions that make up their chosen instrument. An adequate description of the content of a questionnaire can allow clinicians to use their experience to decide if the variables measured, are important to patients. Alternatively they may cite articles which show that the instrument used measures factors that are of clinical importance to the population studied.

b. Are the measurement properties of the instrument adequate?

The measurement properties of the instrument should be considered. The validity, reliability and responsiveness should all be examined. The clinician should have at least a basic understanding of these terms before he or she can draw any conclusion from results. Clinical papers frequently quote instrument validation and responsiveness testing.

Responsiveness measures how well a questionnaire detects small changes in patient status. In clinical trials an unresponsive instrument could give false negative results, and fail to detect health improvements after treatment. Care should be taken to look at the type of instrument that was chosen. A generic questionnaire used to cover each health domain may fail to do so in enough depth to be responsive. Questions may be so superficial as to miss even the most important symptom changes related to the study. On the other hand, a disease specific or domain specific questionnaire may be more appropriate, but likewise this type of questionnaire used out of context of its intended target population will be unresponsive.

Validity aims to show that the instrument measures what it intends to measure, and not some other factor. Clinicians should look for evidence of validity in the study, and in its absence are entitled to scepticism over its measurement of QOL.

c. Are there important aspects of HRQOL that have been omitted?

Investigators may have addressed HRQOL issues, but not done so comprehensively. A paper may examine one specific area of outcome but fail to consider the broader impact of a disease on patients' lives. There would be little weight to a study, for example, that looked at antidepressant treatment, but failed to assess mood or a study may look at a primary area of symptomatology, but fail to measure the functional or social impact of a disease. An example could be measurement of abdominal pain and bowel function in patients with colorectal carcinoma, but failure to examine physical or emotion function. Obviously each case should be considered in context, as a more or less exhaustive approach to assessment may be appropriate.

1.4.3 Interpretation of the results

How clinicians should interpret the final results from HRQOL studies is not always self evident. For example, patients with acute back pain prescribed bed rest had a mean score on the Owestry Back-Disability Index (OBDI), 3.9 points worse than controls (Malmivaara *et al.*, 1995). Is this difference trivial, small but important, of moderate magnitude, or does it constitute a large and extremely important difference between treatments? Investigators can and should help by relating changes in HRQOL to well known functional measures, to clinical diagnostic subgroups (e.g. change in score needed to move a patient from one subgroup of disease to another), to the impact those changes have on daily life or even how they relate to major life events such as family illness, loss of job or bereavement (Testa *et al.*, 1993). Studies that relate the observed changes to changes in more familiar or objective measures can be easier to interpret. Whatever strategy, if investigators don't provide some indication of how to interpret the changes, either directly through comparison with a reference or control population, or by citing previous work, then findings will be of limited use to the clinician. It is often more informative to know the proportion of patients who achieve small, medium or large gains, rather than simple change in QOL.

It should also be noted that statistical significance does not always imply clinical significance. Statistical significance tests are concerned solely with examining the observed data values, to determine whether differences or changes can be attributed to chance and patient variability, or whether there is sufficient evidence to claim there is almost certainly a pattern in the data. Highly significant p-values indicate little about magnitude of differences, and tell us only that the differences are

probably real as opposed to chance events. They tell us even less about clinical significance of the observed changes. In large clinical trials, sample size means that even a small change in QOL will be detected and be found to be highly significant. However, despite being highly significant in statistical terms, the observed difference in QOL might in fact be so small as to be clinically unimportant. The converse is true for small studies; barely significant changes may be exceedingly important in clinical terms.

1.4.4 Applying results to patient care

As we mentioned earlier, patients with the same disease often vary markedly in the QOL they experience. We used the example of one individual with Crohn's disease who may hold down full-time employment, have an active family and social lifestyle, while another patient with the same disease extent and severity may be depressed, unemployed and unable to fulfil their role in the home environment. To truly assess what impact an improvement of QOL might have for an individual patient, the study should examine problem areas similar to those of the patients we treat. The clinician should aim to find out what problems their patient is currently experiencing, the importance he or she attached to those problems and the value they might attach to having them ameliorated. Put in simple terms, this should make us reflect on the process of communication. Like any area of clinical research, a clear understanding of the condition and the patients we treat, is key to the practical application of those results.

1.4.5 Conclusion

In conclusion, the interpretation of QOL results remains essentially qualitative (Fayers and Machin, 2000). Clinical significance is subjective and often a matter of opinion. The values and beliefs of individual clinicians and patients will differ. Thus for a QOL measurement scale, it is unlikely that a single threshold value will be universally accepted as a cut-off-point that separates clinically important changes from trivial or unimportant ones. It is also likely that patients may consider changes in some aspects of QOL to be more important than others. A change of 5 points on one scale may be as clinically important as a change of 20 in another. However, many investigators are finding that for a variety of scales assessing overall QOL and dimensions, changes of between 5% and 10% are noticed by patients and regarded as significant (Osoba, 2002).

Chapter 2

Postcholecystectomy Syndrome

2.1 Epidemiology

Gallstones are one of the most common surgical problems encountered in Western society. In Great Britain post mortem studies have shown a very definite increase in prevalence over the last 25 years (Bateson, 2000). This is supported by studies from Europe (Acalovschi *et al.*, 1987) and North America. Prevalence in the UK is estimated at approximately 20-25% in females and 10-12% in males aged between 40 and 60 (Godrey *et al.*, 1984; Heaton *et al.*, 1991; Bates *et al.*, 1992), and steadily increases with age. These figures are largely based on necropsy studies, but are supported by several large ultrasound based studies from Europe. The Multicentre Italian Study of Cholelithiasis (MICOL) examined nearly 33,000 subjects aged 30 to 69 years, and showed overall gallstones rates of 18.8% in women and 9.5% in men (Attili *et al.*, 1995a).

2.2 Postcholecystectomy syndrome

Laparoscopic cholecystectomy is now widely accepted as the 'gold standard' surgical treatment for gallstones. Figures vary as to the percentage of patients who will continue to have persistent symptoms following surgery. The term 'postcholecystectomy syndrome' has been used to describe this condition, although

the term 'persistent postcholecystectomy symptoms" is probably more accurate. More recently the term "postcholecystectomy pain syndrome" is in vogue. Papers have quoted relief rates of between 65 (Peters *et al.*, 1991; Bates *et al.*, 1991; Qureshi *et al.*, 1993) and near 95% (Wilson and Macintyre, 1993; Luman *et al.*, 1996) for patients having surgery. The large variation may be explained because the characteristics of symptoms attributable to gallstones are often poorly defined and inaccurately measured, and may be assessed at different time points postoperatively. Words such as dyspepsia and flatulence can mean different things to different people, so the method of evaluation and patient mix will greatly affect the measured relief rates. QOL measurement is an example of how patient assessment could be standardised to give more reliable and reproducible results.

In their recent paper Berger *et al* (Berger *et al.*, 2003), conducted a large meta analysis to try and evaluate the effect cholecystectomy had on preoperative abdominal symptoms. Using a Medline search from January 1966 to January 2000 and from reference checking, they identified 542 articles and abstracts looking at symptoms after cholecystectomy. Eligibility screening excluded papers where follow-up was less than one year, where patients were less than 18 years old, when patients had an extraordinary risk of complications e.g. diabetes mellitus and where comparison could not be made between pre and postoperative symptoms. After further quality assessment only 23 articles were available for analysis. This large number of excluded publications highlights why we have such widely differing relief rates reported.

From the included papers, they showed consistently high relief rates after cholecystectomy for 'biliary pain', defined as severe pain located in the upper

abdomen or epigastrium lasting for 15 minutes to 5 hours (Schoenfiled *et al.*, 1988). The pooled relief rate from the 10 studies in which it could be assessed was 92% (95% confidence interval 86 to 96%). They also showed that those patients treated electively did significantly worse than those treated in the acute stages of the disease. Relief rates were 72% and 86% respectively. Nine of the studies looked at symptoms of dyspepsia. Dyspepsia was defined as three or more of either belching, flatulence, nausea, intolerance to fatty food, bloating of the abdomen, epigastric discomfort or acid regurgitation. Relief rates were heterogeneous and ranged from 46% (Fenster *et al.*, 1995) to 89% (Radecke *et al.*, 1993). Talley *et al* has previously reported placebo response rates of almost 70% in patients with functional dyspepsia (Talley *et al.*, 1991), which was comparable to the average of the studied papers. We also know that upper abdominal pain presenting to the general practitioner, disappears without intervention within 1 year in around 70% of patients (Muris *et al.*, 1993). These two factors alone could explain the observed differences with these dyspeptic type symptoms.

They concluded that the methodological quality of the studies in their review was low which would have affected the accuracy of the measurements. They felt that in these cohort studies it was difficult to confirm that any improvement in symptoms was exclusively as a result of surgery. They did not find any randomised placebo controlled trials evaluating the effects of cholecystectomy on preoperative abdominal symptoms. This they felt was due to the ethical dilemmas that surrounds sham operation (Horng and Miller, 2002). They suggested a proper evaluation of the effectiveness of cholecystectomy in terms of symptomatic relief required a

randomised controlled trial, comparing outcomes in symptomatic gallstone patients undergoing either cholecystectomy or simple watchful waiting.

This was carried out in 2002 by a Scandinavian group, who prospectively looked at patients with symptomatic gallstones (Vetrhus *et al.*, 2002). They recognised that for many years it has been an accepted practice that symptomatic gallstones are potentially harmful and should be treated aggressively (Mayo, 1911; Ransohoff and Gracie, 1993). Long-term follow-up in several large epidemiological studies, have shown that the majority of individuals with gallstones remain asymptomatic throughout life (Glambek *et al.*, 1989; Friedman, 1993; Attili *et al.*, 1995b), and Vetrhus *et al* therefore questioned whether this aggressive management was brought about; more through common practice rather than evidence based medicine. They stated that the indication for cholecystectomy in symptomatic patients had never properly been addressed. In their study, 338 patients were considered for inclusion, but after assessment only 137 of these were randomised to either observation or surgery. Of the 156 who were not randomised, 79 (51%) had strong personal preference regarding their treatment method. There was a low dropout rate of 9, and median follow-up was 67 months. Their results showed that of the 69 randomised to observation, 35 (51%) subsequently underwent cholecystectomy and that the cumulative risk of having a cholecystectomy seemed to level off after approximately 4 years. This may indicate that symptoms abate over time, and similar trends have been noted by others (Friedman, 1993). Since the purpose of their paper was to examine the feasibility of observation in patients with symptomatic gallstones, they did not look at the rates of persistent symptoms after surgery in detail. They concentrated rather on complications rates following surgery (6%) and gallstone

related complications in the observational group (4%). They recommended that patients should be informed that watchful waiting was a safe option.

In a later publication using data from the same study group (Vetrhus *et al.*, 2004), the authors focused on pain and quality of life measurement. They unexpectedly found a significant reduction in pain and increase in QOL for both groups after 6 months, which was maintained until 60 months, at the end of the study period. There was no significant difference between the two. They suggested that gallstones may in fact have a more benign course than previously surmised, and this may be one possible explanation for their findings. Regarding methodology, they used two generic QOL questionnaires in the study, which may not have had sufficient responsiveness in this particular disease. Small but important differences in QOL may have been completely missed between the two groups. To help in their interpretation, and to corroborate some of the findings from the Berger paper (Berger *et al.*, 2003), it would have been useful if the authors had examined and discussed outcome in terms of individual symptoms that were affected by surgery, alongside the global QOL scores.

One other important paper published after Berger's review, was an article in the World Journal of Surgery (Peterli *et al.*, 2000) in 2000. They compared the prevalence of postcholecystectomy symptoms with open cholecystectomy during the pre-laparoscopic era, to those with laparoscopic cholecystectomy 4 years after the introduction of the technique. On the one hand they surmised that there may be fewer symptoms after the introduction of the laparoscopic technique because of the advantages it has in terms of fewer adhesions and scar related problems. On the other,

they thought that an increase may be measured because of the more liberal use of laparoscopic cholecystectomy for functional disorders. The latter was supported by papers showing a very definite increase in cholecystectomy rates over the previous decade, without a parallel rise in the prevalence of gallstones (Logorreta *et al.*, 1993; Steiner *et al.*, 1994). The study was well designed and the techniques used for patient assessment were consistent for the two groups despite the 5 year gap between recruitment times. Pain was measured using the Visick Score (Visick, 1948), Visick I, no symptoms; Visick II, minor symptoms without interference of daily activities; Visick III, symptoms not relieved by care and influencing daily activities; Visick IV, symptoms not improved or relapse. This graduated type of scale was probably of more use than a simple VAS, and was chosen to aid with interpretation of results. A detailed history of preoperative symptoms was also recorded which included site and character of the pain, gastrointestinal symptoms (e.g. bloating, diarrhoea and flatulence) and a history of complications (jaundice, pancreatitis and cholecystitis).

Results showed no significant difference between the two groups in the prevalence of abdominal symptoms. One year postoperatively, 90% of patients after open and 94% after laparoscopic cholecystectomy had no or minor abdominal symptoms. They concluded that the prevalence of post-cholecystectomy symptoms did not change with the introduction of the laparoscopic technique. In a similar way to Berger *et al*, they found that following open cholecystectomy, patients with typical biliary type pain had a better long term outcome than those with dyspeptic symptoms. However, they could not show a similar correlation following the laparoscopic technique. As we mentioned earlier, one could speculate that the advantages of minimally invasive surgery, compensated for the potential negative affect of an

increased number of cholecystectomies performed on patients with functional disorders.

2.3 Pathophysiology of postcholecystectomy syndrome

2.3.1 Background

Postcholecystectomy syndrome represents a wide variety of conditions with overlapping symptoms and often poses a diagnostic dilemma for surgeons and gastroenterologists. To help with management its pathophysiology can be considered in terms of structural or functional disease, either within or outside the biliary system. Among the most common causes are persistent or recurrent disease within the biliary system e.g. retained CBD stones or biliary strictures following surgery. These surgically remediable causes are usually identified easily and should be treated appropriately. There are other well defined entities to explain ongoing or recurrent symptoms which are more unusual, and are often difficult to detect or diagnose with certainty. These conditions are discussed below.

To help put them in context, they must first be seen in relation to the prevalence of abdominal symptoms among healthy individuals. A large epidemiological study carried out in Denmark in 1994 looked at abdominal symptoms in the general population (Kay *et al.*, 1994). In an age and sex stratified sample of 4,581 people, they found that 13% of subjects frequently suffered from dyspeptic symptoms and as many as 54% complained occasionally. When they examined abdominal pain they found that over a one year period the prevalence was 30-50%, with 10% having frequent severe episodes. Most symptoms were not persistent or chronic, and there was a large resolution rate of 27-47%. Twice as many women with

abdominal pain consulted their doctor, and they suffered pain episodes significantly more frequently than men, and at a younger age. Remarkably only 15% of men and 10% of women did not experience any abdominal symptoms within the 12 month study period. When we consider only those with severe symptoms, then we can not expect a cure rate from any therapy to treat abdominal symptoms of more 85-90%.

2.3.2 Duodenogastric reflux

In 1996 Farsakh *et al* suggested the role of duodenogastric reflux and bile salt induced gastritis after cholecystectomy, as a causative factor in the development of postcholecystectomy syndrome (bu Farsakh *et al.*, 1996). In their prospective study of 30 patients they compared symptoms, endoscopic findings and gastric bile acid levels pre and postoperatively. They found a positive correlation between the severity of symptoms in postcholecystectomy syndrome and increased bile salt concentrations. Interestingly, all those with typical biliary colic pain had resolution of symptoms after surgery, while dyspeptic symptoms only improved in around 40%. 17% of patients showed an increase in symptoms after surgery and those with gastric ulcers and gastric erosions had a higher mean change in bile salt concentration after surgery. The results appear to confirm a positive correlation, however, the numbers were small and the authors recommended a larger trial to confirm their findings. They also suggested controlled trials to examine the effects of prokinetic drugs and cytoprotective agents on the symptoms of postcholecystectomy syndrome. Latterly, papers have suggested that Helicobacter Pylori may have a synergistic role in development of gastric pathology after cholecystectomy. Zullo *et al* (Zullo *et al.*, 1998) showed a higher

incidence of bile reflux, gastric metaplasia and helicobacter infection rates in cholecystectomized patients.

There is still considerable debate as to the true nature of gastroduodenal reflux and its role in postcholecystectomy patients. Some studies have shown no increase in bile reflux after surgery (Manifold *et al.*, 2000), while others have confirmed Farsakh's initial findings (Fountos *et al.*, 2003). A study by an Egyptian group showed evidence of gastroduodenal reflux in biopsy specimens of gastric antral mucosa one year after cholecystectomy for gallstones (bdel-Wahab *et al.*, 2000). There has been some data published on the use of prokinectics and gastro-protective agents as treatment measures. Erythromycin (Fountos *et al.*, 2003), sucralfate and the proton pump inhibitor rabeprazole have been shown to be of benefit (Santarelli *et al.*, 2003).

2.3.3 Cystic duct remnant

As I have mentioned, there are several possible mechanical explanations for the development of postcholecystectomy syndrome, one of which is retained bile duct stones. A more unusual cause however is from a retained stone or stones within the cystic duct stump. A recent paper from an Irish group discussed 4 cases of retained cystic duct stones causing postcholecystectomy syndrome (Shaw *et al.*, 2004). Each case was treated surgically with resection of the residual cystic duct stump and all had resolution of symptoms. The presence of a cystic duct remnant is defined as a residual cystic duct greater then 1 cm in length. Studies have shown that the majority of these patients are asymptomatic (Lewicki *et al.*, 1973; Larmi *et al.*, 1975). It has also been

reported that the cystic duct remnant infrequently causes symptoms in the absence of other pathologic conditions in the common duct, primarily stones (Hopkins *et al.*, 1979; Rogy *et al.*, 1991). The incidence of symptoms from a cystic duct remnant is unknown, but with the introduction of laparoscopic cholecystectomy and the policy of close gallbladder dissection, this may have resulted in an higher number of reported cases. The common practice during laparoscopic cholecystectomy is to ligate the cystic duct close to the infundibulum of the gallbladder. This technique minimises the risk of damage to the common bile duct, but is likely to result in a longer cystic duct remnant being left behind.

Symptoms can occur months or even years after cholecystectomy, and the remnant is thought to cause symptoms by harbouring residual stones, by developing painful neuromas or by having continued chronic inflammation. In some rare cases, they have been associated with enteric fistulae (Woods *et al.*, 1992) and with Mirizzi's syndrome (Sowula and Groele, 1999). In cases where a cystic duct remnant is thought to be factor, an MRCP should be considered. It has been shown to be superior to USS and ERCP at identifying stones within the cystic duct stump (Rubini and Dimonte, 1999; Shaw *et al.*, 2004).

2.3.4 Sphincter of Oddi dysfunction

Sphincter of Oddi dysfunction (SOD) has been highlighted as one other possible mechanism for postcholecystectomy pain (Evans *et al.*, 1995; Desautels *et al.*, 1999). The sphincter of Oddi is a smooth muscle structure surrounding the distal common bile duct (CBD), pancreatic duct and ampulla of Vater. It traverses the

second part of the duodenum obliquely and is almost entirely situated within its wall (Tzovaras and Rowlands, 1998). It functions independently of the duodenal musculature and acts to control the delivery of bile and pancreatic secretions. It also diverts bile to allow storage in the gallbladder and prevents retrograde reflux of duodenal contents (Becker, 1993). Over the last decade there has been a wealth of articles published that link SOD with biliary and pancreatic type symptoms. Recently it has been classified into two subgroups (Chuttani and Carr-Locke, 1993; Toouli, 1996). Firstly, sphincter of Oddi stenosis which is a structural abnormality due to inflammation or fibrosis. Most common causes include pancreatitis, passage of gallstones through the sphincter and surgical trauma. The second type is sphincter of Oddi dyskinesia, which is an intermittent functional blockage resulting from spasm or hypertrophy of the sphincter muscle. It can be associated with other functional disorders of the GI tract including irritable bowel syndrome (IBS) (Evans *et al.*, 1995). Both types have a raised basal sphincter pressure, but unlike sphincter of Oddi stenosis, this can be reversed in dyskinesia by administering smooth muscle relaxants.

Cholecystectomy may reveal symptoms of previously undiagnosed SOD because there is no longer a gallbladder present to accommodate volumetric and pressure changes within the biliary system (Lisbona, 1992). It has been proposed that CBD dilatation after cholecystectomy is a feature of SOD with a high predictive value for favourable outcome after sphincterotomy (Venu and Geenen, 1986; Thatcher *et al.*, 1987). However this finding is non specific since CBD diameter varies with age (Coelho and Wiederkehr, 1996) and is detected in around 4 percent of asymptomatic patients after cholecystectomy (Graham *et al.*, 1980). There is some objective evidence to support the association between SOD and postcholecystectomy syndrome.

Morphine induced sphincter of Oddi spasm and increased CBD pressure have been shown to induce pain in symptomatic postcholecystectomy patients but not in controls (Tanaka *et al.*, 1985). In another recent prospective series Bozkurt *et al* showed that based on manometry findings, endoscopic sphincterotomy was beneficial in patients with biliary pain after cholecystectomy (Bozkurt *et al.*, 1996).

The diagnosis and treatment of SOD is complex and a detailed review is outside the remit of this thesis, but patient assessment should be based on a range of tests that include USS, endoscopic retrograde cholangiopancreatograophy (ERCP), manometry which is considered the 'gold standard' (Toouli *et al.*, 1986), and provocation studies (Nardi and Acosta, 1966; Belsito *et al.*, 1977; Coelho and Wiederkehr, 1996). All procedures on the sphincter should be undertaken with caution only after careful investigation and patient selection (Tzovaras and Rowlands, 1998).

2.3.5 Psychological factors and somatisation disorders

Psychological factors may be important in the development of postcholecystectomy syndrome. They have already been shown to be common in patients with functional digestive disorders (Drossman *et al.*, 1999), and some studies have looked at the relationship between psychological status and poor outcome after cholecystectomy. Patients with postcholecystectomy syndrome have a higher incidence of anxiety (Markert, 1991) and depression (McMahon *et al.*, 1995), and a higher intake of psychotropic medications (Luman *et al.*, 1996). An Italian group (Lorusso *et al.*, 2003) looked at this issue in detail. Consecutive patients referred to their hospital for laparoscopic cholecystectomy were assessed for inclusion. They

were screened for symptoms of dyspepsia, which were not characteristic of typical biliary colic or gallstone induced symptoms. They broadly defined dyspepsia based on criteria established by an international working team (Barbara *et al.*, 1989). Symptoms were classified as episodic or persistent and referable to the proximal gastrointestinal tract (e.g. upper abdominal pain or discomfort, postprandial fullness, abdominal bloating, belching, early satiety, anorexia, nausea, vomiting, heartburn and regurgitation) or referable to the lower gastrointestinal tract and overlapping with IBS. All patients had organic disease other than gallstones excluded. From the 124 patients screened, 58 (46.7%) were identified with gallstones and dyspepsia. Prior to surgery, and at one year after surgery, psychological and gastrointestinal symptoms were assessed using validated questionnaires. They used the Hopkins Symptom Checklist (SCL-90-R) (Derogatis, 1983) for psychological evaluation and the Gastrointestinal Rating Scale (GSRS) (Svedlund *et al.*, 1988) for digestive symptoms. Patients who did not improve scored significantly higher in all subscales of the SCL-90-R, and in the dyspeptic and total scores of the GSRS. Logistic regression analysis was used to evaluate the association between baseline psychological factors and outcome after surgery. All but two subscales of the SCL-90-R were significant predictors for poor outcome after cholecystectomy.

This was the first study of its type to use validated QOL instruments to investigate how preoperative psychological factors affected outcome after cholecystectomy. Its results confirmed a strong negative association between the two, and backed up finding of earlier papers published on the subject (Jorgensen *et al.*, 1991; Borly *et al.*, 1999). The authors suggested that because the criteria for surgery are perhaps insufficiently rigorous, and patients' expectations of symptom recovery

are sometimes unrealistic, those patients with gallstones should be carefully evaluated before laparoscopic cholecystectomy. They felt that a joint psychological and gastrointestinal assessment was required preoperatively in those with gallstones and dyspepsia. This highlights why Talley (Talley, 1995) and Lumen (Luman *et al.*, 1996) caution against cholecystectomy in patients with prominent symptoms of dyspepsia and other functional digestive symptoms, even though gallstones are present.

Some believe that the syndrome could form part of a somatisation disorder (Stefaniak *et al.*, 2004). Somatisation is defined as repeated presentation of physical symptoms, together with persistent request for medical investigations, in spite of negative findings and reassurances by doctors that the symptoms have no physical basis (World Health Organisation, 1992). Psychological factors such as rumination and social factors such as inadequate social support are thought to contribute to this persistence of somatoform pain (Weisberg and Clavel, Jr., 1999). Brosschot and Thayer state that worry and rumination contribute to both the onset and prolongation of medically unexplained somatoform pain. They speculate that this negative thought process of illness may stimulate a feed forward process, where progressively more illness cues are perceived despite the absence of somatic pathology (Brosschot and Thayer, 2004). It is already widely accepted that social support has a significant influence on pain, anxiety and recovery following surgical procedures (Neuling and Winefield, 1988; Kulik and Mahler, 1989). In addition, House *et al* state that more socially isolated or less socially integrated individuals are less healthy, psychologically and physically (House *et al.*, 1988).

Stefaniak *et al* (House *et al.*, 1988; Stefaniak *et al.*, 2004)hypothesised that patients with postcholecystectomy syndrome would report more rumination and less social support. They looked at patients undergoing surgical treatment for gallstones. From the 212 who completed the study, they found that 20 (12.3%) had persistent symptoms after surgery. None showed evidence of demonstrable organic pathology to explain this. Using linear regression analysis they could demonstrate that patients with ongoing symptoms had a significantly lower level of social support, measured on a social support scale adapted from the FACIT index (29.78 v's 34.94; $p<0.001$). Rumination about themselves also showed higher levels in the symptomatic group, but was not shown to be significant. Like Lorusso *et al* (Lorusso *et al.*, 2003), they suggested that examining psychological parameters may be helpful in preoperative evaluation and postoperative diagnosis for gallstone patients, especially in those dissatisfied with the results of surgery.

2.3 Asymptomatic gallstones

Since the introduction of laparoscopic cholecystectomy, there has been a worldwide increase in the number of cholecystectomies performed (Logorreta *et al.*, 1993; Lam *et al.*, 1996). With improved risk-benefit ratios, this may reflect a lower threshold for intervention by surgeons or a higher demand for this minimally invasive procedure by patients. It may also be partly due to increased use of routine ultrasound scan (USS), for the investigation of abdominal pain. This in turn has led to the identification of incidental gallstones in a higher number of patients. Ransohoff *et al* followed up 139 patients identified with incidental gallstones on USS (Ransohoff and Gracie, 1993). 15 patients (11%) developed symptoms suggestive of biliary colic over

the next five years, and only 6 proceeded to cholecystectomy for biliary symptoms. It was concluded that USS detected coincidental gallstones were infrequently clinically significant.

It is largely accepted that the majority of patients who are symptomatic from gallstones should be treated (Ransohoff and Gracie, 1993), but there is considerable debate as to whether the indication should extend to those who have no symptoms (Schwesinger and Diehl, 1996). Epidemiological studies suggest that the natural history of asymptomatic gallstones is relatively benign, with the majority of patients having no trouble throughout life (Glambek *et al.*, 1989; Friedman, 1993; Attili *et al.*, 1995b). Symptoms occur at a rate of approximately 1-4% per year, reaching 20% at 20 years with fewer complications in later years (Barbara *et al.*, 1987; Friedman *et al.*, 1989; Strasberg and Clavien, 1993). Complications are almost always preceded by symptoms (Thistle *et al.*, 1984; McSherry *et al.*, 1985; Friedman *et al.*, 1989).

Several studies have tried to use objective measurements to predict the progression to symptoms or to severe complications such as cholecystitis, jaundice and pancreatitis in asymptomatic gallstone patients. A French group looked at measurements such as the number and nature of gallstones, gallbladder wall thickness and contractility, and demographic details such as age, sex and co-morbid history. They found none of these to be significant predictors of outcome in patients with asymptomatic stones (Capron and Franco, 1992).

These Figures lend support to the expectant management of most patients with coincidental gallstones, and certainly when cost-effective analysis is considered the

argument is strengthened (Friedman, 1993). There are no prospective randomised trials of therapy, either surgical or medical for asymptomatic gallstones. However decision analysis models have shown no benefit of prophylactic cholecystectomy. In one study, for example, decision analysis was used to compare prophylactic cholecystectomy with expectant management in patients with asymptomatic gallstones (Ransohoff *et al.*, 1983). Prophylactic cholecystectomy slightly decreased survival and was not associated with any appreciable gain in discounted life years. This study was performed prior to the introduction of laparoscopic cholecystectomy, but based on sensitivity analysis included in the study in it doubtful whether this would significantly alter results.

In contrast, a Turkish group recently published a paper that questioned the merit of conservative treatment of asymptomatic gallstones (Mentes *et al.*, 2001). In the first paper of its kind, they used a QOL instrument to compare outcomes of symptomatic and asymptomatic gallstone patients after laparoscopic cholecystectomy. They showed a significant improvement in QOL in both the symptomatic (113.42±21.9 vs. 80.32±19.1 preoperatively; $p<0.05$) and asymptomatic group (113.30±15.2 vs. 96.37±14.26 preoperatively; $p<0.05$). Despite a higher mean preoperative QOL score, there was still a measurable QOL improvement after surgery for the asymptomatic patients. These results challenge those of previous publications, and question the benign nature of gallstone disease. The authors suggested that gallstones perhaps are not truly 'silent', and that insidious symptoms such as bloating, fullness or vague dyspepsia are more tolerable to the patient and as a result more difficult to measure. Their study showed that after surgery these symptoms can improve, and patients have significant QOL improvement. Methods used in previous

studies may not have been sensitive enough to measure subtle preoperative symptoms, or demonstrate small but significant QOL improvement after surgery (Glambek *et al.*, 1989; Attili *et al.*, 1995b). One criticism however, is that follow-up was only for 4 months, and the 'placebo effect' of surgery could explain many of these findings.

Despite the findings of Mentes *et al*, it is still largely accepted that asymptomatic patients are treated expectantly. There are a number of specific circumstances however, where it could be argued that prophylactic cholecystectomy is justified in an asymptomatic patient. These can be largely divided into two groups. Firstly, those at high risk due to certain co-morbid disease (e.g. diabetes, liver cirrhosis, sickle cell disease) and secondly those at risk of developing carcinoma. The most widely studied group of patients that apply, are those with diabetes mellitus. Landau *et al* (Landau *et al.*, 1992) found that patients with diabetes had a higher incidence of infected bile, gangrenous changes and perforation of the gallbladder. They also showed that the mortality rate following surgery for acute cholecystectomy was significantly higher (21%vs9%). This and other papers prompted early cholecystectomy for diabetic patients (Landau *et al.*, 1992; Schwesinger and Diehl, 1996; Patino and Quintero, 1998). This has however largely fallen out of favour. Evidence has shown that for diabetics the morbidity and mortality rates for biliary surgery are comparable to non-diabetics (Aucott *et al.*, 1993; Babineau and Bothe, Jr., 1995). So it is now largely agreed that the magnitude of risk, and the risks and cost of cholecystectomy do not warrant prophylactic cholecystectomy in diabetics with asymptomatic gallstones. One study identified 70 patients with gallstones and diabetes mellitus (Del *et al.*, 1994). They were followed up for five years; 47(70%) were asymptomatic at time zero. During follow-up 10% of asymptomatic patients

developed biliary colic, and 4% developed gallstone related complications. This is similar to that of the general population (Gracie and Ransohoff, 1982; Barbara *et al.*, 1987). In view of this recent evidence, adult diabetics with silent or incidental gallstones should be managed expectantly, and prophylactic surgery is not routinely recommended (Aucott *et al.*, 1993; Del *et al.*, 1994; Babineau and Bothe, Jr., 1995).

Gallbladder carcinoma is rare except in certain high risk ethnic groups e.g. native American Indians. There is a strong correlation between gallstones and gallbladder carcinoma. The risk is approximately four times higher for those with, than in those without, gallstones. The risk increases when gallstones are equal to, or greater than, 3cm in diameter and in patients with gallbladder polyps larger than 10 mm (Lowenfels *et al.*, 1989). Despite this association prophylactic cholecystectomy is not generally indicated (Gibney, 1990). Since the overall prognosis for gallbladder carcinoma is very poor, it is suggested that prophylactic cholecystectomy is carried out for silent gallstones in areas where gallbladder carcinoma in prevalent (Bosmans *et al.*, 1990; Meshikhes, 2002). A porcelain gallbladder is a pathological condition characterised by calcification of the gallbladder wall. It deserves special mention, due to the high incidence of associated gallbladder carcinoma (15-25%) (Berk *et al.*, 1973; Shimizu *et al.*, 1989). This has led many surgeons to practise prophylactic cholecystectomy in this small subgroup of patients.

Finally what of incidental gallstones found at the time of surgery for other abdominal conditions? Again management strategies are controversial, but at least two studies have tried to answer this question. Both showed a significantly higher early (within 6 months) complication rate attributable to gallstones which weren't

removed at initial surgery (Thompson *et al.*, 1984; Saade *et al.*, 1987) .They showed that concomitant cholecystectomy added minimal morbidity to the operation, and for this reason some authors accept that incidental cholecystectomy is safe during gastrointestinal surgery, unless specific contraindications exist (Juhasz *et al.*, 1994).

2.4 Irritable bowel syndrome and gallstones

Functional gastrointestinal disorders (FGID) are defined as "a variable combination of chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities" (Talley *et al.*, 1991). They encompass a wide variety of syndromes attributed to dysfunction of the oesophagus, stomach, small and large intestine, and biliary tract. A recent multinational consensus document was published examining the classification, pathophysiology and treatment options for this complex group of disorders (Drossman, 1999). Patients with FGID's can report a wide variety of symptoms. Often conditions coexist and symptoms overlap between different anatomical regions of the gastrointestinal tract. Categorising these into distinct syndromes or subgroups helps in their diagnosis and treatment (Drossman, 1999).

Among the two most common FGID's, are IBS and functional dyspepsia (FD). They account for 40-60% of referrals to gastroenterology outpatients (Jones *et al.*, 2000). IBS comprises a group of functional bowel disorders in which abdominal discomfort or pain is associated with disordered defaecation or change in bowel habit. It affects between 10-20% of the adult population (Drossman *et al.*, 1997; Talley and Spiller, 2002) and has a female preponderance. Its incidence is unaffected by race or

age. Several scoring methods have been developed to aid diagnosis and treatment assessment. Firstly, in 1978 the Manning criteria (Manning *et al.*, 1978) and more recently, the Rome II criteria (Thompson *et al.*, 1999). These criteria have been drawn up as a consensus rather than a rigid set of rules. Many patients with abdominal pain and altered bowel habit do not fit these criteria exactly, but would still be classified as having a functional disorder.

As mentioned above, there can be considerable overlap of symptoms between FGID's. FD refers to persistent or recurrent pain or discomfort centred in the upper abdomen, with the absence of organic disease. Dyspepsia can occur commonly in patients with symptoms otherwise compatible with IBS (Dotevall *et al.*, 1982; Talley *et al.*, 1992). It is also accepted that patients can have both functional dyspepsia and IBS, or have upper abdominal discomfort exclusively related to IBS (Talley *et al.*, 1999). This overlap can make diagnosis and treatment difficult. The aetiology of these conditions is poorly understood. It is unlikely that IBS reflects an intrinsic disease of the colon, but rather a central neurological dysfunction which can manifest with symptoms in several organ systems. This is supported by its strong association with stress and anxiety, and with many patients exhibiting abnormal illness behaviour and an increased incidence of somatic complaints (Drossman, 1999; Jones *et al.*, 2000).

It has been reported in the past that patients with IBS have a higher incidence of cholecystectomy compared to those without (Fielding, 1977). It is suspected that many of these operations are unnecessary, and that surgery is actually performed for asymptomatic gallstones. IBS can manifest with upper abdominal symptoms, difficult to distinguish from gallstones and patients subsequently undergo surgery that is not

indicated. In a large epidemiological study, a UK group explored this important area (Kennedy and Jones, 2000). Their paper described the prevalence of cholecystectomy and IBS in a sample of British adults in Teeside. They recruited almost 4500 patients to their study, from six general practice registers in the area. IBS was defined as abdominal pain on more than six occasions in the previous year, along with three or more of the Manning criteria. Patients were asked to complete a symptoms questionnaire that had previously been utilised and then validated (Jones and Lydeard, 1992). The response rate to the postal survey was 72%, and data was analysed from 3169 questionnaires (1451 men, 1718 women).

The 12 month prevalence of IBS was 17.2%, with a female to male ratio of 2.2:1. IBS was more common among younger women, and showed a smaller sex difference in the older age groups. Cholecystectomy was also more common in women than men (4.1% vs. 1.3%). Of the 549 patients with IBS, 109(20%) had consulted their general practitioner regarding at least one IBS symptom in the previous two years. There was a gradient in the prevalence of cholecystectomy, which was lowest in subjects without IBS (2.4%), higher in those with IBS who had not consulted (3.9%), and highest in those with IBS that had consulted (7.5%). Substantial differences in health beliefs and psychopathology are known to exist between patients with IBS who consult, and those who do not (Kettell *et al.*, 1992). With this in mind, these results are all the more striking. The explanation for this increased incidence is not entirely clear from the study, and further research was recommended. We could speculate that higher attendance with IBS leads to increased referral for specialist opinion, and subsequent surgery. This is undoubtedly a significant factor, but is unlikely to be the full explanation for the observed difference.

Those with IBS, who did not attend, also had a higher cholecystectomy rate compared to the normal population. This suggests some other underlying mechanism might also be to blame. Possibly altered motility in IBS predisposes to gallstone formation (van Erpecum and van Berge-Henegouwen, 1999), or if we consider the mechanisms behind FGID's, there may be background physiological changes to account for symptoms in both the gastrointestinal and biliary systems (Kellow *et al.*, 1999).

Chapter 3

Quality of Life and Gallstones

3.1 Introduction

Despite the large number of routine cholecystectomies carried out in the UK each year for gallstones, there is a relative paucity of published material looking at QOL following surgery for this benign disease. Hepatobiliary conditions in general are lacking good quality research in this area, highlighted by the low number of disease specific questionnaires available. In the majority of medical specialities the balance of published data is weighted towards patients with malignant disease. In general this large group of patients have reduced life expectancy and QOL in the terminal phases of life is of high priority and its measurement has been used regularly for many years. This trend has meant less focus on quality of life measurement following surgery for benign conditions, and outcomes have looked at things such as length of hospital stay, complication rates and disease recurrence rates.

3.2 QOL and gallstones in the literature

This observation is true also for gallstones and their surgical treatment. Using the keyword search headings "quality of life", "gallstones", and "cholecystectomy" on Medline from 1966-2005 and from cross referencing; only ten English language papers have been published which relate to QOL and gallstones. One paper is the

validation study for the GIQLI (Eypasch *et al.*, 1995) which will be discussed in detail in chapter 5. The remaining 9 papers are summarised in Appendix 1, and are discussed in turn below.

There has been an exponential rise in the measurement of QOL in medicine recently, and it is not surprising that most of the published papers relating to gallbladder disease spans only the last 5 years. One paper however stands out as being earlier, and would appear to have been well ahead of its time. A Dutch group (Plaisier *et al.*, 1994) published the paper in 1994. It was a small randomised study of 49 patients and compared the treatment of gallstones by either ESWL or traditional open surgery. Lithotripsy is a method of stone fragmentation using ultrasonic waves (Sauerbruch *et al.*, 1986; Ertan, 2002). Nowadays it is commonly used for the treatment of renal stones, but has lost favour in the management of gallstones due to poor stone clearance rates (Sackmann *et al.*, 1991) and recurrent stone formation (Sackmann *et al.*, 1994; Pelletier *et al.*, 1995). It was done at a time when laparoscopic cholecystectomy was still in its infancy, but becoming popular and ESWL was being evaluated as an alternative mode of therapy for those unfit for the open procedure.

At the time, Plaisier *et al* cited the theoretical disadvantages of ESWL over the gold standard open surgery as being the main reason why QOL was a suitable outcome measure rather than merely stone clearance rates. They felt that any form of elective surgery was directed primarily towards improvement of QOL and should be the most important aim of intervention. They referenced a British Journal of Surgery review paper (Fraser, 1993), suggesting that health status-analysis was particularly

well suited in the area of minimally invasive surgery. Unlike most other QOL studies of that time they used a well validated questionnaire. Early QOL studies in surgery and other related fields often relied on simple visual analogue scales or self assessment questionnaires that were either not validated, widely used or even inappropriate to the intervention being measured. It was around that time that the MOS 36-item short-form health survey (SF-36) was published (Ware, Jr. and Sherbourne, 1992). It gained popularity and raised the awareness of appropriate QOL measurement instruments. It quickly became the benchmark from which all other instruments were measured and is still a widely used generic instrument, particularly in the gastroenterology literature. For their study they chose a translation of the Nottingham Health Profile (NHP) (Hunt *et al.*, 1981; Ware, Jr. and Sherbourne, 1992) . It was one of the first QOL instruments developed well before the SF-36 in the late 1970s. It was originally intended for use in epidemiological studies comparing health status among populations rather than individuals. It measures six dimensions: physical mobility, pain, sleep, energy, social function and emotional reaction. Each of these dimensions contain questions requiring a 'yes' or 'no' answer (dichotomous). If questions are answered 'yes', the patient's score will be high which indicates a poor QOL. At the time it was one of the few well validated questionnaires and scoring was weighted, so that a positive response for each item was multiplied by a factor before aggregation. Health gain was defined as a reduction in the median score. As opposed to the SF-36, the NHP has limited responsiveness and when used in a clinical setting results should be interpreted with caution (McEwen and McKenna, 1996). For this reason it could be argued that the SF-36 may have been a more useful instrument to use in this type of study, but at that time I suspect a Dutch translation was not available.

The design of the study was good. Patients were asked to complete the NHP before and at 3, 6, and 12 months after treatment. This method of repeated questioning is often used in QOL measurement to ensure reliable data collection. Rather surprisingly they claimed a 96% completion rate for the questionnaires, which is well above the 70-75% expected rate for most mail surveys (Quintana *et al.*, 2003a) and what I have experienced from my own research. It was initially intended that 160 patients would be recruited to the study, but after a six month period where no patients were consented to randomisation the trial was stopped. In the end they included 49 patients, 23 randomised to ESWL and 26 to conventional surgery. The low numbers may have in part been explained by their strict inclusion and exclusion criteria, but they admitted that the study took place at a time when laparoscopic cholecystectomy was becoming popular. They claimed that this fact alone severely hampered recruitment. Their results showed a more profound and significant improvement in QOL in the open cholecystectomy (17.1% improvement, $p=0.003$) group compared with those that had ESWL (10.5% improvement, $p=0.113$) particularly in pain, energy and emotional reaction. They concluded that the NHP was a useful tool in general surgery even when the numbers were small. They also concluded that in terms of QOL improvement, open surgery was preferred to ESWL, particularly when laparoscopic cholecystectomy was not feasible. In those unwilling or unfit for surgery they stated that ESWL was an adequate form of treatment because most patients have a measured QOL improvement. As discussed previously, they may have been able to show a more significant change in QOL following ESWL if they had chosen the SF-36 as the main instrument.

Almost 7 years later a Portuguese group revisited QOL measurement in patients undergoing ESWL (Carrilho-Ribeiro *et al.*, 2002). The aim of their study was to compare QOL in patients who had previously successful ESWL and who had no sign of recurrent stones, to a group of matched patients treated at the same time with ESWL but who eventually underwent cholecystectomy for treatment failure. From the outset, in terms of QOL measurement their study design was poor. Firstly they only took a snapshot measurement of QOL using the now well validated GIQLI (Eypasch *et al.*, 1995). The GIQLI is a disease specific questionnaire concentrating on mainly digestive type symptoms. It consists of 36 questions each scored from 0 to 4, giving a maximum of 144 points. Healthy controls have been shown to score a mean of around 120 to 130. Taking only one measurement at a protracted period from intervention (in some cases up to 8 years) limits the way their results should be interpreted. Health related quality of life (HRQOL) is a dynamic psychological variable that can vary from day to day, and be influenced by factors such as additional illness that may develop later or even personal problems or socio-cultural events that can not be controlled by researchers. It makes no sense to record QOL such a long time after intervention when these factors cannot be accounted for. In order to obtain reliable data, measurements should have been taken at regular intervals following treatment. In addition there was no random assignment, so pre-treatment QOL should have been taken to control for possible differences in pre-treatment levels.

Secondly, questionnaires were completed by the main author using telephone interview. Telephone interview is generally regarded as a poor technique for data collection. Patients may feel less at ease to answer the questions honestly and they may also feel they have to 'say the right thing', particularly when the interviewer is

their primary physician. This method therefore raises the question of bias. The third criticism of the study is that their numbers were small, with only 18 patients in each group. As mentioned above, they were not randomised and the only difference between the groups was that those who underwent cholecystectomy had a failure of ESWL. The authors admitted that a bias in favour of those successfully treated with ESWL could not be ruled out.

Despite their results showing no significant difference in either total QOL scores for both groups (128 ESWL vs. 124 Surgery / p=0.33) nor in any of the sub-domains, they claimed that the ESWL group had a better QOL when the 8 questions examining dyspepsia were examined in isolation. As you would expect their conclusions were vague, stating there might be a higher rate of long-term dyspepsia with gallbladder preserving treatments. A prospective randomised study using QOL to compare gallbladder conserving treatment such as ESWL and laparoscopic cholecystectomy was never performed.

Plaisier *et al* published another QOL paper in 1995 (Plaisier *et al.*, 1995), where they prospectively measured QOL in patients after laparoscopic and open cholecystectomy. The follow-up period was for one year and was started at a time when the benefits of laparoscopic over open cholecystectomy were being studied. They again used the NHP for QOL assessment, and with a combination of postal questionnaires and telephone surveys, they managed a 96.5% return rate. However, their recruitment numbers were small (14 in the laparoscopic group and 17 in the open group). They were able to demonstrate a similar significant improvement in QOL in both groups after surgery, which reached its maximum earlier in the laparoscopic

group. They concluded that this was more circumstantial evidence that laparoscopic cholecystectomy was superior to open surgery.

In 2002 a Turkish group also published a paper comparing long-term QOL after laparoscopic and open cholecystectomy (Topcu *et al.*, 2003). They had large numbers of patients in each group and used the SF-36 and GIQLI for QOL measurement. The use of two instruments is a well recognised method of strengthening data collection and improving sensitivity. It is particularly valuable when the criterion validity of one questionnaire is being checked against another (usually the 'gold standard' index). In this case both questionnaires were already well validated at the time of the study and the authors' aim was to increase sensitivity by using both a generic (SF-36) and disease specific (GIQLI) questionnaire. The aim of their study was to identify any difference in QOL between the two groups and to use QOL as a factor for determining the 'gold standard' therapeutic modality for cholelithiasis. They pointed out that at that time, laparoscopic cholecystectomy was already widely accepted as the 'gold standard' treatment supported by published morbidity and mortality rates, and data which consistently reported benefits over open surgery including reduced post-operative pain, shorter hospital stay, better cosmetic results , more rapid recovery and immunological benefits during the early post-operative period (Soper *et al.*, 1992; Troidl *et al.*, 1992; McMahon *et al.*, 1994; Hackam and Rotstein, 1998). There were, however, no published QOL studies supporting this, and they felt that QOL was an important criterion that could strongly influence the patient's and surgeon's choice of operation.

Unfortunately their method and timing of administration of the questionnaires were poor, and were heavily criticised in later publications (Lachinski *et al.*, 2004). Similar to the Portuguese group, they failed to randomise patients or to check pre-operative QOL scores as a baseline, and they only checked QOL at one time point with a mean of 41 to 56 months after the primary procedure. Surprisingly, they showed a significant difference in all domains of the SF-36 in favour of laparoscopic surgery. In terms of symptomatic improvement as measured by the GIQLI, there was no overall advantage between the two techniques. As mentioned, the paper was heavily criticised (Lachinski *et al.*, 2004). Firstly, and probably rather unfairly, Lachinski *et al* questioned the merit of measuring QOL in patients with gallstones. They said that although fashionable at the time, QOL was probably not the most appropriate psychological parameter for differentiation between two groups of patients suffering from a medical problem that is not likely to have a profound affect on QOL. Although QOL was especially important for chronic conditions (Makarewicz *et al.*, 2003; Kalso *et al.*, 2003), they claimed that its use in acute conditions was moderate at best. Certainly, from the most recent publications on the QOL and gallstones (Mentes *et al.*, 2001; Quintana *et al.*, 2003a; Vetrhus *et al.*, 2004), and indeed from my own results, there is a very definite and measurable QOL change after surgery for gallstones which is independent of an acute attack. The most likely reason for not having a measurable change in QOL is because the instrument used was not sensitive enough. In this example, Topcu *et al* used the GIQLI which has been shown to be sensitive in benign gallbladder disease. Admittedly, they failed to use the whole questionnaire, and only administered a cut down version which related only to gastrointestinal symptoms. This may have affected the overall reliability of the index. Lachinski quite rightly felt that QOL, independent of the

operative technique, was unlikely to be affected significantly in the postoperative course after cholecystectomy, particularly with such a protracted time from surgery. Secondly, they criticised the lack of preoperative questioning and lack of randomisation, and warned that these methodological drawbacks compromised the scientific value of the paper. Their explanation for a measurable difference in QOL observed in the study was due to these design faults, and that changes simply reflected pre-treatment differences.

In a recent paper from Norway (Vetrhus *et al.*, 2004), Vetrhus *et al* compared long term QOL between patients undergoing cholecystectomy and those being treated with simple observation. As discussed in detail in the previous chapter, the conservative approach to gallstone management has been extensively studied in terms of symptom free intervals, frequency of recurrent attacks and most importantly the incidence of new complications such as jaundice, pancreatitis and gallbladder carcinoma. This was an important land-mark paper that compared QOL outcome between these two groups. Their aim was to examine frequency and intensity of pain attacks and QOL in patients with symptomatic, uncomplicated gallstones treated with cholecystectomy or observation.

Compared to previous papers (Carrilho-Ribeiro *et al.*, 2002; Topcu *et al.*, 2003), their study design and technique of QOL measurement was good. The study size was reasonable. From 338 patients considered for inclusion, 137 were prospectively randomised to the study (Observation n=69 / Cholecystectomy n=68). QOL was measured at time 0, and at 6, 12 and 60 months using the NHP and the Psychological General Well Being Index (PGWB) (Dupuy, 1984). The PGWB is a

well validated (Wiklund and Karlberg, 1991) generic instrument similar to SF-36. It consists of 22 questions divided into 6 domains (anxiety, depressed mood, positive well-being, self-control, general health and vitality). All items are scored using a 6 point Likert scale, giving a maximum score of 132. Higher scores indicate positive well-being. Interestingly, pain was assessed separately using their own pain score and a VAS. They calculated pain as the sum of responses from 4 items related to gallstone pain (intensity of pain last week, duration of pain last week, frequency of pain in the last 6 months and use of analgesics in the past 6 months). All items were scored using a 5 step Likert scale (0-4), giving a range of 0 to 16. Higher scores indicated more frequent and severe attacks. The VAS represented the intensity of pain during the last week.

Despite being a well designed study, their results were disappointing and difficult to interpret. The NHP showed no significant variation over time between the two groups. The PGWB however did show a significant improvement in QOL at 6 months, but this observed variation was the same in the two randomised groups. The pain scores also improved with time (maximal at 6 months), but again with no difference between the groups. The authors did not expect this finding and made several suggestions as to why this trend may have been observed. Firstly, they suggested that at the time of recruitment, patients were invariably at a higher level of disease activity. Therefore regression towards the mean may be a reason for this change in pain and QOL. Secondly, they raised the question about the natural course of symptomatic gallstones. They theorised that gallstones may in fact have a more benign natural course than previously surmised. Lastly, they questioned the sensitivity of their measuring instruments, which I think is the most likely explanation

for the unusual results. Both the NHP and the PGWB are generic instruments that may not be sensitive enough to pick up minor changes in QOL (Jenkinson *et al.*, 1988) when patients are in a quiescent phase of their disease, a disease specific questionnaire would have been preferable. They mentioned the Gallstone Impact Checklist (GIC) (Russell *et al.*, 1996) but stated that it had not been extensively validated or available to them at the time of their study. The results from the pain scores may also be explained by insensitivity in their non-validated questionnaire. Interestingly however, they did show that patients in the observed group, who had a gallstone related event (e.g. admission due to acute attack or gallstone related complications), had significantly higher pain scores than those who did not.

Mentes *et al* used QOL to compare symptomatic and asymptomatic cholelithiasis before and after laparoscopic cholecystectomy (Mentes *et al.*, 2001). This was an important study which could answer the question raised by other authors, can QOL changes can be measured in asymptomatic gallstones (Vetrhus *et al.*, 2004; Lachinski *et al.*, 2004)? Using strict inclusion and exclusion criteria 67 patients with gallstones were prospectively recruited, and subsequently underwent uncomplicated laparoscopic cholecystectomy. Preoperatively, patients were divided into two groups, symptomatic and asymptomatic. Those deemed symptomatic showed the classical symptoms of cholelithiasis, that is biliary colic. Patients with complications secondary to their gallstones were not included. All patients had gallstones confirmed with ultrasound, and QOL was measured using the GIQLI preoperatively and at 4 months postoperatively. Their results showed a significant increase in the total GIQLI score in both the symptomatic (113.42±21.9 vs. 80.32±19.1 preoperatively; $p<0.05$) and asymptomatic group (113.30±15.2 vs. 96.37±14.26 preoperatively; $p<0.05$). Both

groups also showed significant improvement in all sub-domains of the index except social items which only showed improvement in the symptomatic group. This evidence certainly gives positive weight towards the use of the GIQLI for the measurement of QOL in gallstones patients. Perhaps more importantly, it added some very useful data to support the argument of a more aggressive surgical approach to the management of asymptomatic gallstones. It is certainly the only QOL paper showing improvement after laparoscopic cholecystectomy for patients with asymptomatic gallstones. It is easy to understand how patients with recurrent attacks of severe biliary colic will improve, but this evidence suggested that a more indolent or chronic course might globally influence well-being. They stated that asymptomatic gallstones may not in fact be a truly 'silent' disease, and that patients may be more tolerable of vague abdominal symptoms, especially if they developed gradually, in parallel with chronic gallstone disease. Their follow-up however was only for 4 months, and it could be argued that by showing an improvement in asymptomatic patients, they were simply demonstrating a 'placebo effect' from the surgery.

In 2002 a Danish group published an article in the Lancet where they used QOL as a secondary outcome measure to prospectively compare a wait-and-see policy or laparoscopic cholecystectomy after endoscopic sphincterotomy for bile duct stones (Boerma *et al.*, 2002). They recruited 120 patients to the study, and showed that 47% of patients randomised to a wait-and see policy had recurrent symptoms compared to 2% of the laparoscopic cholecystectomy group. Their use of QOL measurement was poorly planned and is open to several criticisms. They used a questionnaire called the MOS-Short Form General Health Survey (SF-24) (Stewart *et al.*, 1988), which is a generic questionnaire derived from the SF-36 (Ware, Jr. and Sherbourne, 1992). As

discussed already, unless combined with a disease specific instrument such as the GIQLI, this type of questionnaire is unlikely to be responsive enough, particularly in the quiescent phase of this benign disease. Their methods of administration were also questionable. Like the Topcu paper (Topcu *et al.*, 2003), they took a single snapshot of QOL 3 months after the intervention, and failed to take into account variations in preoperative QOL. They introduced controls to the study by comparing QOL in a random age and sex matched population, but surprisingly they used the SF-36 for QOL measurement. Although this questionnaire is obviously similar to the SF-24, there are differences and it is unlikely that data from each is directly comparable. Not surprisingly, they found QOL was unhelpful in the selection of treatment strategy, and I feel this part of their study was poorly thought out and probably just an added extra, since QOL measurement at that time was very popular.

Lorusso *et al* (Lorusso *et al.*, 2003) used QOL to investigate whether psychological symptoms were associated with poor outcome after cholecystectomy, which was discussed in detail in chapter 2. They used the SCL-90-R and the GSRS for analysis and showed that patients with gallstone disease and dyspepsia were unlikely to improve 1 year after surgery if they show psychological distress preoperatively.

The final paper that makes up this series was published recently in the British Journal of Surgery (Quintana *et al.*, 2003a). It is innovative in its approach to QOL measurement, in that is uses data to identify clinical variables that could be used to predict outcome following laparoscopic cholecystectomy. They prospectively recruited patients to this observational study, and measured QOL using the GIQLI and

SF-36 before and after surgery. With some 698 patients matching the inclusion criteria, and successfully completing the questionnaires, this certainly is the largest group of gallstone patients to be recruited to a QOL study. Their method of questionnaire administration was sound, and to maximise response to this postal survey, they contacted non responders on no less that three occasions. Their final uptake rate was a healthy 78.7%. Their data analysis was complex using a multivariate linear regression analysis with improvement in QOL as the dependant variable. Similar to the Mentes study they subdivided the patient group, this time into 6 distinct categories. Patients were first classed as either asymptomatic (10.9%), symptomatic but with uncomplicated gallstones (62.3%) or lastly, symptomatic but with complicated gallstones e.g. pancreatitis, cholangitis or acute cholecystitis (26.8%). These three sub groups were further divided into either low (81.6%) or high risk (18.4%) based on American Society of Anaesthesiologists scores (ASA). This gave a total of six distinct groups of patients. Like Mentes *et al* (Mentes *et al.*, 2001) they found that patients with symptomatic cholelithiasis had the greatest improvements in QOL, especially those with low surgical risk. This improvement when compared to asymptomatic patients remained even after adjustment for co-morbidity and sociodemographic conditions. Asymptomatic patients at high risk were chosen as the reference group because conceptually they seemed to be the least suited for cholecystectomy and furthermore, in adjusted analysis they were shown to experience the least QOL improvement. As one might expect this group was small (2.6% of total), which probably reflected the physicians judgement not to operate on this type of patient. Compared to this group, those patients with complicated or uncomplicated symptomatic cholelithiasis and low surgical risk had greater gains in

most of the sub-domains of the SF-36 and GIQLI. However statistical significance was only reached in the domains of bodily pain and mental health.

They concluded that cholecystectomy was most appropriate for patients at low risk, and with the diagnosis of symptomatic stones, especially those with complicated cholelithiasis. This matched current recommendations regarding appropriateness of cholecystectomy (Johnston and Kaplan, 1993; Johnson, 2001). In contrast to the Mentes paper their results supported a conservative approach to the use of cholecystectomy for asymptomatic stones, particularly in patients at high surgical risk. No previous study had aimed to establish a relationship between patient and disease characteristics and QOL improvements after cholecystectomy in patients with cholelithiasis.

Shortly after its publication, a short letter in response was printed (Aggarwal and Senapati, 2004). It pointed out that the indications for surgery in the asymptomatic group, particularly the high risk reference group, should have been presented. They stated that prophylactic surgery for asymptomatic gallstones was controversial with some favouring expectant management and others selective surgery in those at high risk of complications (Schwesinger and Diehl, 1996), and they felt that the low QOL gains in this group were self-explanatory. They also commented that relief rates in symptomatic patients following cholecystectomy are high in those with typical biliary pain, and lower in those with more vague dyspepsia type symptoms (Berger *et al.*, 2003) and felt it would have been useful to know the distribution of symptoms.

3.3 QOL and gallstones – what next?

Correlation of QOL change with preoperative symptoms in gallstone patients is certainly the next logical step, and it was with this in mind that this study was designed.

Chapter 4

Hypothesis and Aims

4.1 Background

To summarise the discussion in previous chapters, it is apparent that a significant proportion of patients undergoing laparoscopic cholecystectomy for gallstones experience persistent symptoms after surgery (Peters *et al.*, 1991; Bates *et al.*, 1991; Luman *et al.*, 1996). Relief rates range from between 65 and 95%, and the evidence shows that those who exhibit typical biliary pain have a better outcome than those who show atypical dyspeptic type symptoms (Schoenfiled *et al.*, 1988; Radecke *et al.*, 1993; Fenster *et al.*, 1995; Berger *et al.*, 2003). The prevalence of persistent symptoms does not appear to be affected by the surgical technique employed (Peterli *et al.*, 2000). Large Scandinavian and U.S. epidemiological studies have shown that the majority of patients with gallstones remain asymptomatic throughout life (Glambek *et al.*, 1989; Friedman *et al.*, 1989). It is largely accepted that a conservative approach to asymptomatic gallstones should be taken, despite evidence showing that laparoscopic cholecystectomy can be performed with minimal risk (Coelho *et al.*, 2000).

What of treatment for those with symptomatic gallstones? Symptoms occur at a rate of approximately 1-4% per year, reaching a maximum of 20% at 20 years

(Barbara *et al.*, 1987; Strasberg and Clavien, 1993), and serious complications such as pancreatitis, cholecystitis and jaundice are almost always preceded by symptoms (Thistle *et al.*, 1984; McSherry *et al.*, 1985; Friedman *et al.*, 1989). Some research shows that symptoms abate with time (Friedman, 1993). This was supported by Vetrhus *et al* (Vetrhus *et al.*, 2002) who confirmed in their prospective observational study, a low rate of complications (4%) in patients treated expectantly for symptomatic stones, and a cumulative risk of needing cholecystectomy that appeared to level off after 4 years.

It is known that psychological factors play an important role in developing postcholecystectomy syndrome. McMahon *et al* (McMahon *et al.*, 1995) showed that patients who experienced persistent symptoms had a higher incidence of anxiety and depression, two factors that have been well documented in association with IBS and other FGID's (Drossman *et al.*, 1999). Luman *et al* (Luman *et al.*, 1996) suggested that the subgroup of patients who experienced bloating and altered bowel habit and required psychotropic medications may in fact have 'silent gallstones' in the background of IBS. These types of patients are unlikely to benefit from surgery.

Patients with IBS can manifest with symptoms similar to those of gallstones, and higher cholecystectomy rates have been reported (Fielding, 1977). A UK based group showed that patients with IBS, particularly those who consult on a frequent basis have a higher rate of cholecystectomy compared to the general population (Kennedy and Jones, 2000). The exact reason for this increased rate remains unclear. Impaired intestinal motility may predispose IBS patients to gallstones (van Erpecum and van Berge-Henegouwen, 1999), or they may have some underlying physiological

mechanism causing symptoms in both the gastrointestinal and biliary systems (Kellow *et al.*, 1999). Despite these two possible explanations, patients with IBS and other functional gastrointestinal conditions undoubtedly undergo unnecessary surgery for asymptomatic gallstones.

Measuring HRQOL has become an important endpoint to researchers and clinicians and when employed correctly its assessment can help improve quality of care. Recently, Quintana *et al* used QOL to predict outcome in patients following laparoscopic cholecystectomy (Quintana *et al.*, 2003a). They showed that those patients who were symptomatic and at low risk had the highest health gains after surgery. This is the only study to have examined a relationship between preoperative disease characteristics and HRQOL improvement after surgery for gallstones. As already mentioned, the next logical step is to examine preoperative symptoms in gallstone patients and use QOL as a predictor of health improvement.

4.2 Hypothesis

The hypothesis for this study was therefore:

"Patients undergoing laparoscopic cholecystectomy for gallstones do not experience significant quality of life improvement, if they exhibit typical features of irritable bowel syndrome"

4.3 Aims

The aims of this study were:

1. To show that those patients with proven gallstones who express typical features of irritable bowel syndrome preoperatively do not experience a significant improvement in quality of life after laparoscopic cholecystectomy.

2. To use quality of life assessment to identify, preoperatively, a subgroup of patients with known gallstones who may not benefit from operative intervention.

Section 2

METHODOLOGY

Chapter 5

Instrument Selection

5.1 Introduction

As discussed in detail in the first chapter, selection of the correct instrument is a crucial step in designing a QOL study. Certain key elements should be considered if meaningful results are to be obtained. Factors such as target population or disease group, type of instrument, psychometric properties and feasibility of administration should all be considered when choosing an instrument (Guyatt *et al.*, 1993; Moyer and Fendrick, 1998).

5.2 Background

In this study the plan was to examine how QOL was affected after treatment of gallstones by laparoscopic cholecystectomy. It was felt more appropriate to select a disease specific rather than a generic questionnaire, since the primary concern was to measure effects on outcome, and to examine how QOL could be used in treatment prediction. It was also hypothesised that a significant proportion of the patients would be affected by symptoms of IBS, which would be detected more readily if a disease specific questionnaire was used. Generic instruments have been used before in patients with cholelithiasis (Plaisier *et al.*, 1994; Vetrhus *et al.*, 2004). In both these examples criticisms were made about instrument selection. If a disease specific

questionnaire had been chosen, particularly in the Norwegian paper (Vetrhus *et al.*, 2004), more useful information might have been recorded. Disease specific questionnaires tend to be more responsive or sensitive to small changes in a patient's clinical state and they can pick up QOL variations even in patients who are in a quiesant phase of disease.

5.3 The Gallstone Impact Checklist

Firstly, disease specific questionnaires for gallstones were examined. Surprisingly, available QOL data and instruments are lacking for benign hepatobiliary disease, in particular gallstones. There was only one questionnaire published at the time of study design, the 'Gallstone Impact Checklist (GIC)' (Russell *et al.*, 1996). This was published in 1996 and has never been widely accepted or validated. The questionnaire consists of 41 self administered items encompassing 4 sub-domains: food and eating, dyspepsia, emotional impact score and pain sub-score. Using the forward search facility on the ISI web of science internet site, this questionnaire has only been cited 5 times since its publication (Quintana *et al.*, 2003a; Quintana *et al.*, 2003b; Vetrhus *et al.*, 2004; McColl, 2004; Quintana *et al.*, 2005). Each time it was referenced as a disease specific questionnaire available for gallstones, but as one not widely accepted or validated. There were no other published papers that use the GIC as their primary instrument, and it was not listed on the PROQOLID website. This meant that obtaining appropriate copies, translations, scoring guidelines and databases would be difficult. The main reason however for rejecting this questionnaire for the study was its lack of validation. It may have been feasible to use it in parallel with

another questionnaire to give criterion validity, but for reasons stated below this was also declined.

5.4 Instruments used in IBS

Since there were no suitable instruments to look specifically at patients with symptoms from gallstones, focus was turned towards a system specific instrument, ideally one that covered symptoms across a number of gastrointestinal conditions. This could be expected to measure QOL in patients with gallstones, IBS and functional gastrointestinal disorders all of which were important in the design. An instrument with a core set of questions and additional modules for specific gastrointestinal complaints would have been best, but again no such instrument was available. Using one of the already well established generic instruments (e.g. SF36 or NHP) in parallel with one or even two other disease specific instruments was considered. As discussed above, the GIC could have been used in conjunction with a disease specific questionnaire for IBS, for example the 'Irritable Bowel Syndrome – Quality of Life' (IBS-QOL) (Patrick *et al.*, 1998) or the 'Quality of Life Questionnaire for Functional Digestive Disorders' (FDDQL) (Chassany *et al.*, 1999). The FDDQL in particular stood out as a possible candidate. It was developed in 1999, as a single disease specific questionnaire suitable for the measurement of HRQOL in IBS and FD. It comprises 43 items that cover areas of daily activity, anxiety, diet, sleep, discomfort, coping and control of disease. Its validity and reliability were established in an international cross sectional study of 401 patients with IBS and FD (Chassany *et al.*, 1999) where it correlated well with the SF-36. It was unclear whether the FDDQOL would be suitably responsive to detect symptom improvement

in patients following laparoscopic cholecystectomy since it had never been used in the context of gallstones or post-cholecystectomy syndrome. To ensure suitable symptom coverage would mean using the FDDQOL alongside the GIC. A generic instrument such as the SF-36 would also be needed for validation of the GIC. This gave a total of three instruments consisting of 120 items that would take approximately 40 minutes to complete by patients. Several of the questions overlapped or were very similar between questionnaires. This, alongside the obvious burden of time placed on the patient, could significantly affect compliance, and to expect patients to complete all three questionnaires on at least 4 separate occasions was unrealistic. Interpretation of three questionnaires would also be difficult, especially when one questionnaire remained largely unvalidated.

5.5 The Gastrointestinal Quality of Life Index

Attention turned to look for a single questionnaire that was already validated, and had enough responsiveness for use across multiple gastrointestinal conditions. At the time only one questionnaire was available to measure HRQOL across multiple gastrointestinal disorders, the Gastrointestinal Quality of Life Index (GIQLI) (Eypasch *et al.*, 1995). The questionnaire contains 36 items, scored on a five point Likert scale from 0-4, giving a total score from between 0 and 144 (Appendix 2). Higher scores measure a more favourable response and report a higher QOL. In contrast with the GIC, this questionnaire had been extensively validated (Eypasch *et al.*, 1995; Nieveen van Dijkum *et al.*, 2000) , and was being used routinely in clinical research across different gastrointestinal conditions (Sailer *et al.*, 1998; Slim *et al.*, 2000; Mentes *et al.*, 2001; Freys *et al.*, 2001; Granderath *et al.*, 2002). Interestingly,

the authors originally planned to have a set of core questions applicable to any patient with gastrointestinal disease along with several small organ specific modules. Through their three phase development however, they decided on a single questionnaire which could be subdivided into 5 subscales: core symptoms, physical items, psychological items, social items and disease specific items. In phase II of development, construct validity was supported by demonstrating correlation with a global index, the 'Spitzer Quality of Life Index' (SQLI) (Spitzer *et al.*, 1981; Troidl *et al.*, 1987), and a disease specific scale, the 'Bradburn Affect Balance Scale' (BABS) (Bradburn and Noll, 1969) that measures emotional well-being. During phase III, they showed good test re-test reliability with an interclass correlation coefficient of 0.92 when the questionnaire was applied to 25 clinically stable patients at two time points 48 hours apart. It also showed excellent internal consistency measured by Chronbach's Alpha (>0.90). During responsiveness testing, they chose patients undergoing laparoscopic cholecystectomy for biliary colic as their study group. In 194 patients who underwent laparoscopic cholecystectomy, a significant improvement was observed from a mean score pre-operatively of 87.3 to 111.7 six weeks postoperatively ($P<0.0001$), showing that this questionnaire was sufficiently responsive for use in patients with cholelithiasis. This made the GIQLI particularly appealing for use in this study.

5.5.1 The GIQLI and gallstones

Following its publication, it has been used in several studies to examine QOL in patients with gallstones; these were discussed in detail in chapter 3. A Spanish group published an article using the GIQLI as a predictor of outcome in patients

grouped according to their anaesthetic risk (Quintana *et al.*, 2003a). In another article, Mentes *et al* looked at QOL following laparoscopic cholecystectomy for symptomatic and asymptomatic gallstones (Mentes *et al.*, 2001), and showed that the GIQLI has sufficient responsiveness to detect changes in health status following surgery for not only symptomatic, but also asymptomatic stones. Finally, after a recent consensus conference Korolija *et al* recommend the GIQLI as the primary HRQOL assessment tool for use in gallbladder disease (Korolija *et al.*, 2004).

5.5.2 The GIQLI and IBS

The GIQLI has been used in at least one study of patients with IBS (Coffin *et al.*, 2004). They measured QOL in 858 patients with IBS, and found significant correlation between symptom intensity and change in QOL. QOL measurement in IBS patients is not a new practice, and it isn't surprising that this index has not been used more frequently because four disease specific questionnaires are available for the condition (Hahn *et al.*, 1997a; Patrick *et al.*, 1998; Wong *et al.*, 1998; Chassany *et al.*, 1999). The questionnaire has also been used in a broad spectrum of gastrointestinal disorders, such as perforated peptic ulcer (Joneja *et al.*, 2004), gastric bypass surgery (Lee *et al.*, 2004b), anal incontinence and constipation (Damon *et al.*, 2004), gastro-oesophageal reflux (Granderath *et al.*, 2002; Kamolz *et al.*, 2003) and chronic pancreatitis (Witzigmann *et al.*, 2002).

5.6 Final selection

The basic criteria for selecting an instrument were listed in chapter one, and when considered in relation to this study are all fulfilled. The GIQLI has a significant amount of data available concerning its validity, reliability, sensitivity and responsiveness. The questionnaire has been used before in the target population and indeed, part of its psychometric testing involved gallstone patients. Since the questionnaire was to be used in isolation, the length was appropriate and the chance of compliance maximised. Finally, the questionnaire was published and validated in an appropriate language and sufficient reference data and interpretation guidelines were available.

5.6.1 Authors permission

A copy of the questionnaire, user manual and database was downloaded from the PROQOLID website, and permission to use the questionnaire was obtained in writing directly from the author, Professor Ernst Eypasch, Department of Surgery, University of Cologne, Germany.

Chapter 6

The Preoperative Assessment of IBS

6.1 Introduction

In this study it is important to identify preoperatively patients suffering from FGID's, particularly those with IBS. The diagnosis of IBS and other functional disorders is based on symptom evaluation (Mearin *et al.*, 2004b). A multinational consensus document was recently published, and classified this diverse group of disorders according to anatomic region (Drossman, 1999). They also outlined diagnostic criteria for each of the disease groups. Distinguishing between disorders can however be difficult. Many of the symptoms of IBS for example overlap those of FD (Talley *et al.*, 1999).What can make diagnosis more difficult is that symptom types can vary with time and in intensity (Mearin *et al.*, 2004a).

6.2 The Manning criteria

The term IBS was first coined in 1944 by Peters and Bargen (Peters and Bargen, 1944). Initially thought of as a disease of exclusion, it soon became clear that for clinical and research purposes a more rigid set of diagnostic criteria were needed. Bristol researchers subsequently reported a group of six symptoms that could discriminate people diagnosed with the disorder from those with documented structural bowel disease. These became know as the Manning criteria (Manning *et al.*, 1978) (Table 1). Since each of these symptoms also occurs with organic disease, in isolation they are neither sensitive nor specific indicators of IBS. However, the greater

the number of symptoms, the higher the likelihood of having IBS. No recommendations were given for a threshold number of symptoms to make a positive diagnosis, so subsequent studies used two, three or four symptoms as a definition. The Manning criteria were corroborated in a study by Talley *et al* (Talley *et al.*, 1990), where they compared symptoms in groups with IBS, organic disease and non-ulcer dyspepsia as well as in healthy controls. A significant incidence of symptoms attributed to IBS was noted in all groups, again indicating the lack of specificity of these symptoms.

Table 1. *The Manning Criteria (Manning et al., 1978)*

1. Abdominal pain relieved by defaecation
2. Pain associated with looser stools
3. Pain associated with more frequent stools
4. Sensation of incomplete rectal emptying
5. Passage of mucous
6. Visible abdominal distension

6.3 The Rome and Rome II criteria

A consensus based approach was adopted in an attempt to standardize the assessment criteria for IBS. In 1989 an international group of experts met in Italy at the XIII International Congress of Gastroenterology and developed the "Rome Criteria" (Thompson *et al.*, 1989; Drossman *et al.*, 1990) (Table 2). This helped standardise entry levels into clinical studies and allowed investigators to compare their results with confidence. The Rome criteria included the symptoms listed by Manning *et al*, but also specified the chronicity term "continuous or recurrent" to take into account the nature of IBS which is persistent and relapsing. It also added more symptoms concerning altered defaecation. After some modification (Drossman *et al.*, 1990), it stated that patients must have one of the pain symptoms present for ≥3 months, along with three or more of the altered defaecation patterns for ≥25% of the time. This classification was quite complex, and while suitable for research purposes was not easily applicable to clinical practice. For this reason it was again modified and simplified in 1999 to the "Rome II Criteria" (Thompson *et al.*, 1999) (Table 3). It stated that patients should have 12 weeks of discomfort in the preceding 12 months or have two of the pain symptoms present. They recommended that the second group of criteria included in Rome I were supportive rather than mandatory, and stated that the validity of the symptom criteria was supported by patient studies (Manning *et al.*, 1978; Thompson, 1997; Longstreth, 1997), by factor analysis on populations (Whitehead *et al.*, 1990; Taub *et al.*, 1995), and on long term patient follow-up (Harvey *et al.*, 1987).

Table 2. *Comparison of Rome Criteria and Revised Rome Criteria*

Rome Criteria (Thompson *et al.*, 1989)	**Revised Rome Criteria** (Drossman *et al.*, 1990)
Continuous or recurrent symptoms of: Abdominal pain relieved with defaecation or associated with a change in frequency or consistency of stool *and/or* Disturbed defaecation (two or more of): • Altered stool frequency • Altered stool form (hard or loose/watery) • Altered stool passage (straining or urgency, feeling of incomplete evacuation) • Passage of mucous *Usually with* • Bloating or feeling of abdominal distension	*Continuous or recurrent symptoms for at least 3 months of:* Abdominal pain or discomfort relieved with defaecation or associated with change in frequency or consistency of stool *and** An irregular (varying) pattern of defecation at least 25% of the time (three or more of): • Altered stool frequency • Altered stool form (hard or loose/watery) • Altered stool passage (straining or urgency, feeling of incomplete evacuation) • Passage of mucous • Bloating or abdominal distension **Comment by the committee that the decision to include the pain criterion is to be left to the discretion of the investigators*

Table 3. *The Rome II Criteria (Thompson et al., 1999)*

Pain or discomfort for 12 weeks of the previous 12 months associated with two of the following three:

- Relief with defaecation
- A change in frequency of stool
- A change in consistency of stool

Symptoms that cumulatively lend support to the diagnosis:

- Abnormal stool frequency (>3 bowel movements per day or <3 bowel movements per week)
- Abnormal stool passage (straining, urgency or feeling of incomplete rectal emptying)
- Passage of mucous
- Bloating or feeling of abdominal distension

6.4 The prevalence of IBS using different scoring criteria

This evolving diagnostic approach has meant differences in study definitions of IBS, making comparison between groups difficult. IBS is clearly one of the most frequent explanations for chronic gastrointestinal complaints. True prevalence varies from between 3 and 20% depending on the criteria used (Drossman *et al.*, 1993; Boyce *et al.*, 2000; Saito *et al.*, 2000). A group from Finland recently assessed the prevalence of IBS in a random population of 5000 adults (Hillila and Farkkila, 2004). They used both the Manning and the Rome I and II criteria in their assessment, and

found that prevalence estimates using three of the Manning criteria were significantly higher when compared to either Rome I or Rome II (9.7% vs. 5.6% or 5.1% respectively). Interestingly when only two Manning symptoms were used the prevalence estimates were much higher (16.2%). This corroborated the findings of Saito *et al*, that the Manning criteria identifies a higher number of patients with IBS compared to Rome I (Saito *et al*., 2000). They concluded by saying that it was unclear whether the Rome I or the Manning definition was the better means of identifying patients with IBS, but agreed it was useful to understand the differences between the two in order to interpret the literature regarding it. One argument is that the Manning criteria are in fact more sensitive at identifying cases than either Rome I or Rome II. Hahn *et al* went further and postulated that both the Manning criteria and the Rome I criteria underestimate the true number of sufferers (Hahn *et al*., 1997b).

6.5 Choosing a scoring method

So which should be used? It is clear that these criteria were drawn up as a consensus rather than a rigid set of rules. In clinical practice the diagnosis of IBS is often made by exclusion of organic disease, aided by a lack of "alarm" symptoms such as bleeding and weight loss, and on past experience or clinical intuition. Most general practitioners have never heard of, or use either the Manning or Rome criteria (Thompson *et al*., 1997; Agreus, 2000), and studies have shown poor agreement in the diagnosis of IBS made by them and those identified by the Rome II criteria (Vandvik *et al*., 2004). It would appear that the Rome definition and Manning criteria are too complicated to use in a busy clinical environment. For research purposes however it is

vitally important that validated diagnostic criteria are implemented, so results can be compared with confidence.

Since opinions differ regarding what constitutes the most appropriate diagnostic method, and the evidence shows clear differences in population selection between those that are available, this study will use IBS symptoms applicable to both the Manning and Rome II criteria for diagnosis. This will allow comparison between both scoring methods.

Chapter 7

The Study

7.1 Introduction

After deciding on the most appropriate QOL questionnaire (Eypasch *et al.*, 1995), and on suitable grading criteria for IBS (Manning *et al.*, 1978; Thompson *et al.*, 1999) a plan was formulated to examine how HRQOL outcome was affected following laparoscopic cholecystectomy. This was to be a prospective observational study to measure change in QOL over time and correlate this with preoperative symptoms in order to predict outcome. As discussed in chapter one, the technique of administration of the questionnaires was considered. It was decided that the GIQLI should be completed on at least three separate occasions, once preoperatively and at 6 and 12 weeks postoperatively. This technique is well recognised for obtaining a more accurate representation of QOL change (Langenhoff *et al.*, 2001), but increased frequency of questioning can affect compliance (Fraser, 1993). Since only one questionnaire was employed with a completion time of less than 10 minutes, it was agreed that this would probably not be an issue. A 6 week period after surgery was felt to be a sufficient time to recover from the initial surgical insult, and to give a true measurement of health change. To further strengthen the data it was later decided to include a long term follow-up questionnaire 2 years down the line. For patients unable to complete the questionnaire unaided, an interviewer technique or even proxy data

collection is sometimes instituted (Fletcher *et al.*, 1992). It was felt that this would introduce unnecessary bias to results (Guyatt *et al.*, 1993) so these patients were excluded from the study.

7.2 Patient recruitment

Patients with proven gallstones on USS who were placed on a routine waiting list for laparoscopic cholecystectomy were recruited. Prior approval was sought from the regional ethics committee. Patients were recruited from 3 local hospitals, The Mater Hospital, The Royal Victoria Hospital and Craigavon Area Hospital. Permission to perform the study was obtained from hospital administration as well as the consultants in charge of each patient. It was initially planned to prospectively recruit all patients at the time of booking during their outpatient appointment. Since a significant delay was observed between booking and surgery, patients already on the waiting list were also asked to take part at the time of admission for their surgical procedure. Verbal consent (Appendix 3) was given and each patient was given an information sheet outlining the details of the study (Appendix 4).

At the time of study design there were limited data available on QOL after cholecystectomy and its relationship to preoperative symptoms. There were only two papers published that used the GIQLI as an index, the original validation paper by Eypasch *et al* (Eypasch *et al.*, 1995) and one by Mentes *et al* that assessed symptomatic and asymptomatic cholelithiasis before and after surgery (Mentes *et al.*, 2001). Since follow-up questionnaires were to be administered by post, at least a 30% drop-out rate was expected. Using figures from the previous studies, a simple power

calculation showed a sample size of 110 patients would be sufficient to detect a 10 point change (either increase or decrease) in QOL, and achieve statistical significance to the 1% level. It was decided to aim for a study size of 150 to take into account non responders and those patients subsequently excluded from the study.

7.3 Inclusion and exclusion criteria

Patients were not included in the study if they fulfilled any of the following criteria:

1. Failure to give verbal consent, or agree to postoperative follow-up.
2. Unable to comprehend or complete the questionnaire e.g. blindness, dementia and severe psychiatric illness.
3. Pregnancy.
4. Alcohol or drug abuse.
5. Proven chronic organic disease thought to significantly affect HRQOL status e.g. inflammatory bowel disease, diabetes and bronchitis.

Patients were subsequently excluded from the study if they fulfilled any of the following criteria:

1. Failure to complete the QOL questionnaire preoperatively along with at least one postoperatively.
2. Proven neoplastic disease or gallbladder carcinoma subsequently identified on histopathology.
3. If patients had a significant complication during or as a result of surgery, for example, bile duct injury, bile leak, retained duct stone or infection.

7.4 Controls

Since the questionnaire was administered preoperatively and again postoperatively to calculate change in QOL, patients acted as their own controls.

7.5 Data Collection

After consent for inclusion patients were asked demographic details and questions regarding symptomatology. These were recorded on a detailed pro-forma (Appendix 5) which had been designed to include symptoms relevant to both cholelithiasis and FGID's. It was divided into subheadings which included: previous investigations, details related to pain or discomfort, cholelithiasis, IBS, symptoms of gastroduodenal disorders and brief details of any previous psychiatric illness. There was sufficient detail to allow calculation of both the Manning and the Rome II criteria for IBS. The pro-forma was designed in a simple tick box format to avoid ambiguity and to ensure all relevant details were documented. For certain symptoms that were similar in nature, for example fullness or bloating, a brief explanation of the exact meaning of each was given to ensure they were accurately recorded. The pro-forma was completed by the doctor who booked the patient for surgery or by the person who took consent preoperatively for surgery.

Following the pro-forma patients completed the preoperative GIQLI questionnaire. The technique of answering the questions was explained and it was emphasised that no question should be left blank. To avoid user bias or interference they were asked to fill out the questionnaire unaided. It was then collected before the patient left the outpatient clinic or went for surgery. At three time points after surgery

(6 weeks, 3 months and 2 years) patients were again asked to complete the GIQLI. This part of the study was carried out as a postal survey. In an attempt to improve response rates, questionnaires were sent with covering letters and stamped addressed envelopes. Again, to avoid the issue of bias either for or against the operating surgeon, the questionnaires and letters were addressed from the Department of Surgery, Queens University Belfast, and not from individual hospitals or consultants. At each time point, patients who did not reply within 15 days were sent a second letter and copy of the questionnaire. If they failed to reply for a second time it was presumed they no longer consented to take part in the study and were not contacted further. If patients failed to complete at least one questionnaire following surgery they were excluded. Three months after initial discharge patient records were reviewed, to determine the need for readmission or any significant complication related to or following the procedure.

7.6 Statistical methods

Data was entered into the statistical analysis package SPSS ® Version 12 (SPSS Inc., Chicago, USA). Patients were identified using their unique hospital unit number. From the patient pro-forma, symptoms were recorded as being present, absent or not recorded and given the values 1, 0 or 99 respectively. Similarly, responses to each of the GIQLI questions were recorded from 0 to 4 where 0 was the least favourable response and 4 the best response. Again, missing data was recorded with a value of 99. Outcome was measured in terms of global QOL scores at 6 weeks, 3 months and 2 years. Mean postoperative QOL scores and the 4 domain scores of the index were calculated. Differences between and within groups were analysed using analysis of variance followed by the appropriate paired or independent t-test.

Symptom and outcome correlation was carried out using stepwise linear regression analysis models where mean postoperative QOL was the dependent variable and independent variables were an interaction term of the baseline score before surgery, Manning symptoms, Rome II criteria and the individual symptoms recorded in the patients pro-forma. Summary values are expressed as mean ± SEM and significance was taken at the 5% level ($p<0.05$).

Section 3

RESULTS AND DISCUSSION

Chapter 8

Results

8.1 Recruited patients

One hundred and fifty eight patients were enrolled in the study with a mean age of fifty three years. Thirty five patients (22.2%) failed to complete at least one postoperative questionnaire and were excluded. Five (3.5%) further patients were excluded due to significant postoperative complications (2 with bile leaks requiring drainage, 2 with retained bile duct stones and 1 with a bowel injury). No patients met the exclusion criteria of gallbladder carcinoma diagnosed at histopathology, and there were no deaths in the study group. During follow-up two patients were diagnosed with a significant organic disease (one with metastatic carcinoma and one with inflammatory bowel disease) thought to affect HRQOL and data from these patients were not included.

Therefore a total of one hundred and twelve patients (70.9%) had sufficient data sets for inclusion. This reached the estimated number required to show significance by the previous power calculation. As expected with gallstone disease there was a strong female preponderance. There were ninety eight women (87.5%) and fourteen men (12.5%) in the study giving a female to male ratio of 7:1. The mean ages were 51.5 and 61.4 years respectively. The age range for the group was from 23 to 81 years. Patients were recruited from three local hospitals, 22 (19.6%) from

Craigavon Area Hospital, 49 (43.8%) from the Mater Hospital, Belfast and 41 (36.6%) from the Royal Victoria Hospital, Belfast.

8.2 Comparison of pre and postoperative QOL scores

Patient's global quality of life scores were calculated for the four time points in the study. These will be referred to as Q1 for the preoperative questionnaire and Q2, Q3 and Q4 for the postoperative questionnaires taken at 6weeks, 3 months and 2 years respectively. Mean scores are summarised below in table 4. The mean preoperative score was ***88.8*** ± ***1.3*** (61.7% of 144, the highest score possible with the index) and improved significantly 6 weeks after surgery to ***105.5*** ± ***1.3*** ***(p<0.001)***. This improvement was maintained at 3 months, but at 2 years analysis showed significant regression towards the baseline of ***7.6*** ± ***2.3*** ***(p=0.003)*** points. Mean change in QOL is summarised in table 5.

Questionnaire	Mean	Std. Error	95% Confidence Interval	
			Lower	Upper
Pre-operative (Q1)	88.8	1.3	86.3	91.4
post 6 weeks (Q2)	105.5	1.3	102.9	108.0
post 3 months (Q3)	107.2	1.7	103.8	110.6
post 2 years (Q4)	99.6	1.9	96.0	103.3

Table 4. *Mean QOL Scores Before and After Surgery*

Change in QOL	Mean change	Std. Error	P Value	95% Confidence Interval	
				Lower	Upper
Q1 to Q2	16.7	1.8	<0.001	13.0	20.3
Q1 to Q3	18.4	2.2	<0.001	14.1	22.6
Q1 to Q4	10.8	2.3	<0.001	6.3	15.3

Table 5. *Mean change in global QOL scores*

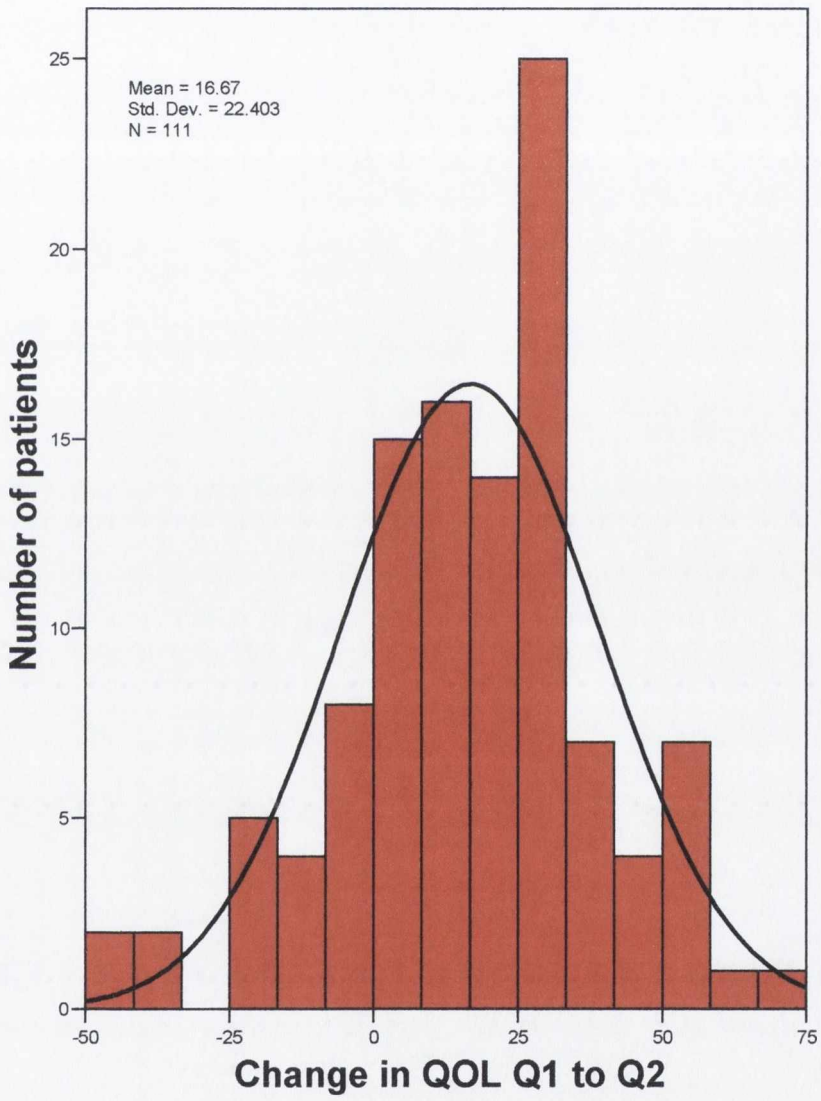


Figure 6. Histogram showing change in QOL between preoperative and 6 week questionnaires

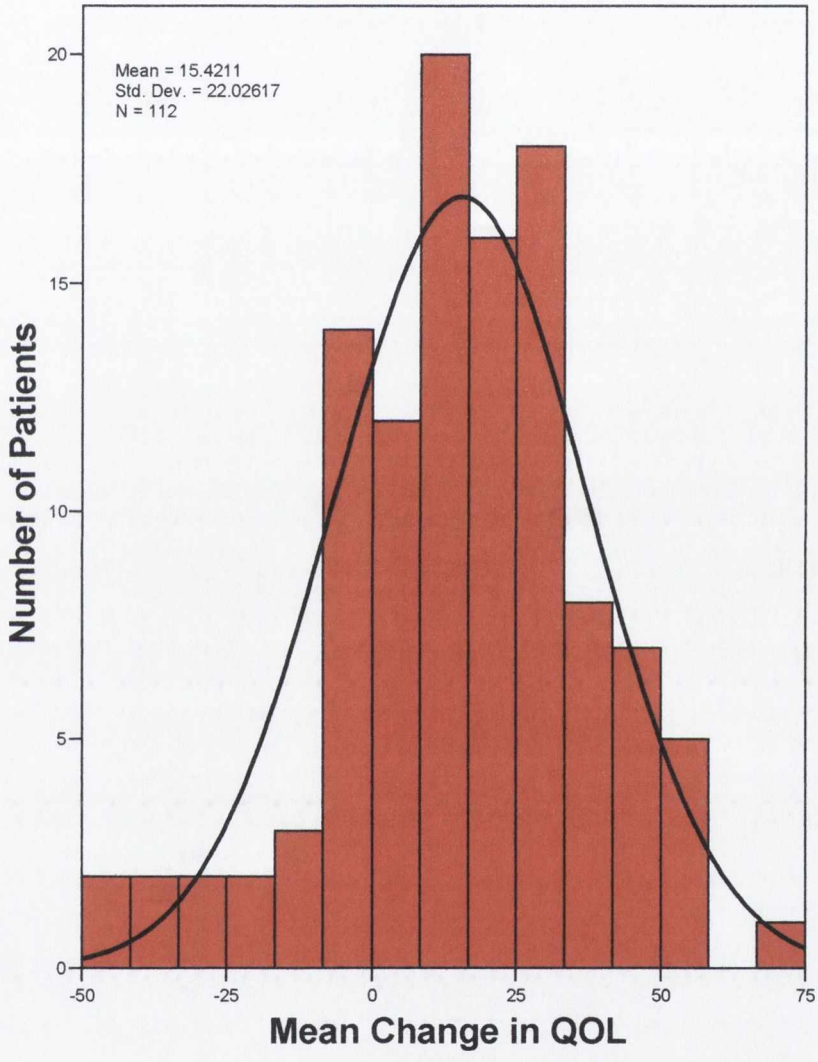


Figure 7. Histogram showing change in QOL between the preoperative questionnaire, and the mean score of all three postoperative questionnaires

8.3 Domain scores

Data for the four sub-domains of the questionnaire were analysed. The ***physical wellbeing*** domain included questions 15 to 21 of the GIQLI (Appendix 2) and had a maximum score of 28. The ***GI symptoms*** domain included questions 1 to 9 and 27 through to the end of the questionnaire; the maximum score for this section was 76. The ***social domain*** consisted of the 5 questions numbered 22 to 26 with a maximum score of 20 and finally the ***emotions*** sub domain was made up of the remaining questions 10 to 14, again with a high score of 20.

8.3.1 Physical wellbeing

This domain showed significant improvement after surgery. The mean preoperative score was ***14.1 ± 0.4*** and increased by around 12% after 6 weeks to ***17.4 ± 0.4 ($p<0.001$)***. This change was maintained to 3 months, but there was partial regression towards the baseline after 2 years ***16.2 ± 0.5 ($p=0.002$)***. These figures are summarised below.

Physical Wellbeing	Mean	Std. Error	95% Confidence Interval	
			Lower	Upper
Pre-operative	14.1	0.4	13.4	14.9
Post. 6 weeks	17.4	0.4	16.7	18.2
Post. 3 months	18.0	0.5	17.0	19.0
Post. 2 years	16.2	0.5	15.1	17.2

Table 6. *Mean physical wellbeing scores before and after surgery*

Change in Physical Wellbeing	Mean change	Std. Error	P Value	95% Confidence Interval	
				Lower	Upper
Q1 to Q2	3.3	0.5	<0.001	2.2	4.3
Q1 to Q3	3.9	0.6	<0.001	2.7	5.1
Q1 to Q4	2.1	0.7	<0.001	0.8	3.4

Table 7. *Mean change in physical wellbeing scores*

8.3.2 GI symptoms

This domain showed significant improvement after surgery. The mean preoperative score was ***50.5*** ± ***0.7*** and increased by 11% after 6 weeks to ***58.6*** ± ***0.7*** ***(p<0.001)***. Unlike the physical domain this improvement in QOL was maintained through to the end of the study period at 2 years ***57.1*** ± ***1.1*** ***(p<0.001)***.

GI symptoms	Mean	Std. Error	95% Confidence Interval	
			Lower	Upper
Pre-operative	50.5	0.7	49.1	52.0
Post. 6 weeks	58.6	0.7	57.1	60.1
Post. 3 months	58.9	1.0	57.0	60.8
Post. 2 years	57.1	1.1	55.0	59.2

Table 8. *Mean GI symptoms scores before and after surgery*

Change in GI symptoms	Mean change	Std. Error	P Value	95% Confidence Interval	
				Lower	Upper
Q1 to Q2	8.1	1.0	<0.001	6.0	10.1
Q1 to Q3	8.3	1.2	<0.001	6.0	10.8
Q1 to Q4	6.6	1.3	<0.001	4.0	9.1

Table 9. *Mean change in GI symptoms scores*

8.3.3 Emotional wellbeing

Emotional wellbeing showed a trend similar to the GI symptoms domain. A statistically significant improvement was measured after surgery and was maintained through to 2 years. The mean preoperative score was ***11.1 ± 0.3*** and increased by 17.5% to ***14.6 ± 0.3 ($p<0.001$)*** after 6 weeks.

Emotional wellbeing	Mean	Std. Error	95% Confidence Interval	
			Lower	Upper
Pre-operative	11.1	0.3	10.5	11.6
Post. 6 weeks	14.6	0.3	14.0	15.1
Post. 3 months	15.0	0.3	14.3	15.6
Post. 2 years	14.1	0.4	13.4	14.9

Table 10. *Mean emotional wellbeing scores before and after surgery*

Change in Emotional Wellbeing	Mean change	Std. Error	P Value	95% Confidence Interval	
				Lower	Upper
Q1 to Q2	3.5	0.4	<0.001	2.8	4.2
Q1 to Q3	3.9	0.4	<0.001	3.0	4.7
Q1 to Q4	3.1	0.4	<0.001	2.1	3.9

Table 11. *Mean change in emotional wellbeing scores*

8.3.4 Social wellbeing

Social wellbeing also showed significant improvement after 6 weeks which was maintained at the 3 month questionnaire. Unlike the other domains however it showed full regression back to baseline at the 2 year time point. The mean preoperative score was ***13.1 ± 0.5*** increasing by 8.5% to ***14.9 ± 0.3 (p<0.001)*** 6 weeks after surgery and returning to ***12.2 ± 0.4 (p=0.05)*** at 2 years.

Social wellbeing	Mean	Std. Error	95% Confidence Interval	
			Lower	Upper
Pre-operative	13.1	0.3	12.6	13.6
Post. 6 weeks	14.9	0.3	14.3	15.4
Post. 3 months	15.4	0.3	14.7	16.0
Post. 2 years	12.2	0.4	11.5	13.0

Table 12. *Mean social wellbeing scores before and after surgery*

Change in Social Wellbeing	Mean change	Std. Error	P Value	95% Confidence Interval	
				Lower	Upper
Q1 to Q2	1.7	0.4	<0.001	1.0	2.5
Q1 to Q3	2.2	0.4	<0.001	1.4	3.1
Q1 to Q4	0.8	0.5	<0.001	-1.8	0.1

Table 13. *Mean change in social wellbeing scores*

Change in mean domain scores after surgery are summarised in Figures 8 & 9 below.

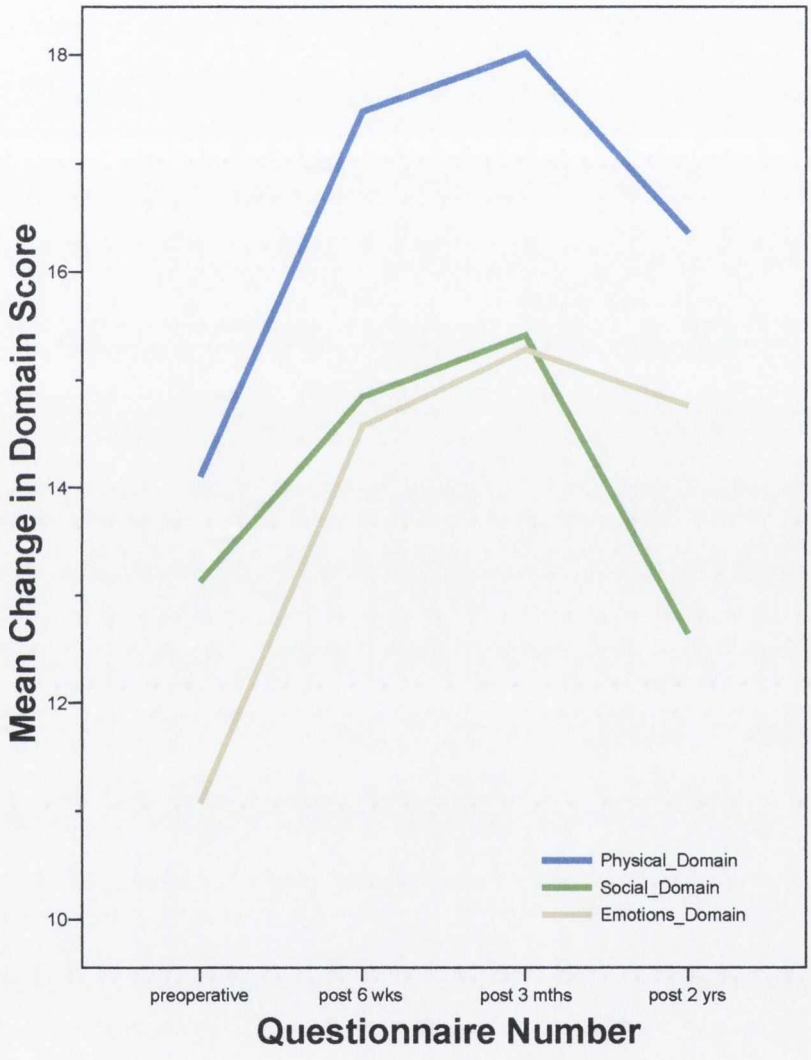


Figure 8. Change in Domain Scores Following Surgery

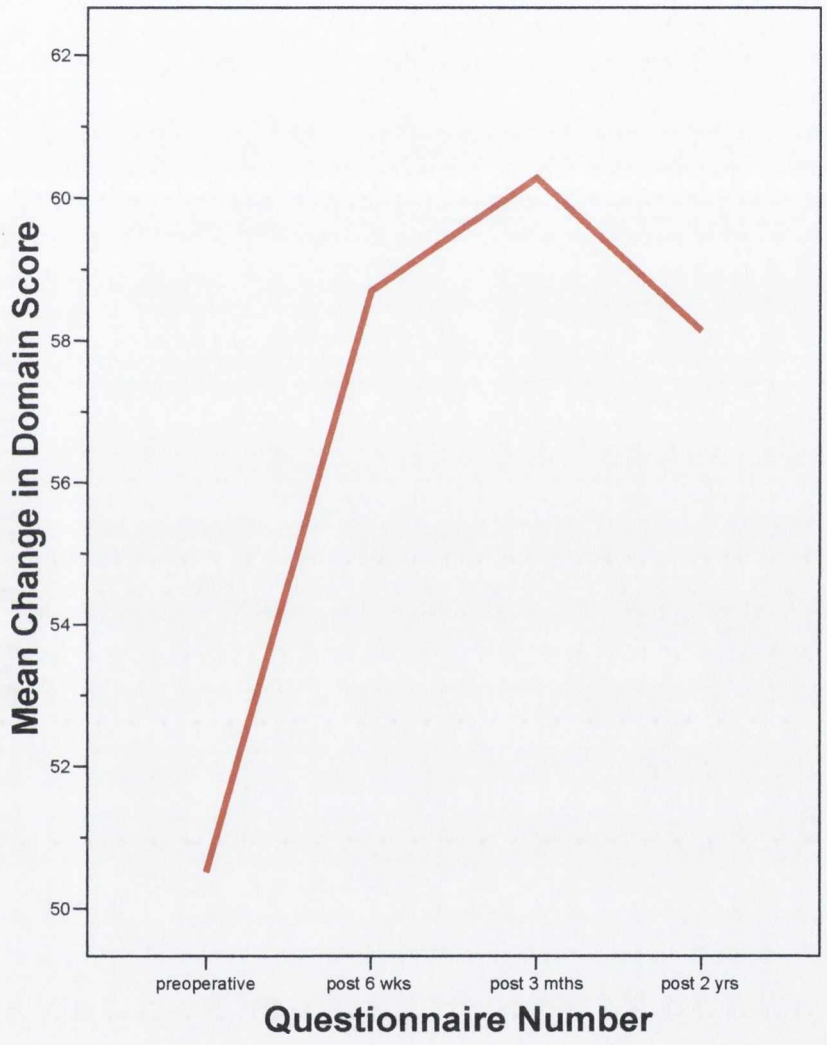


Figure 9. Change in GI Domain Score Following Surgery

8.4 Comparison of Manning scores with change in QOL

At recruitment 32 patients (28.8%) had 2 or more Manning symptoms present. Using stepwise multivariate linear regression analysis, Manning scores were correlated with change in QOL. There was a significant negative correlation of ***-5.2 ± 1.29 (p<0.001)*** points between Manning symptoms and QOL scores after surgery.

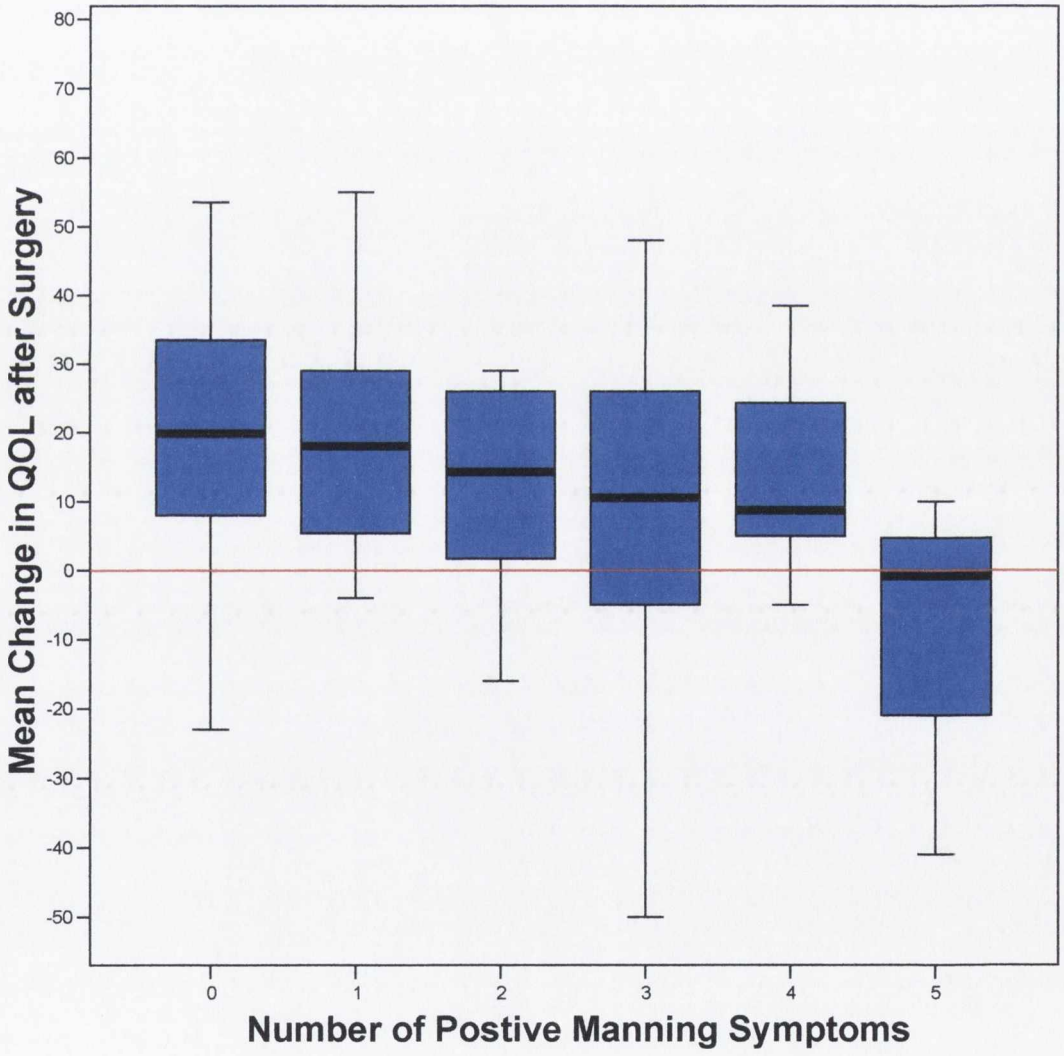


Figure 10. Box plot showing change in QOL vs. numbers of Manning symptoms

8.4.1 Comparison of Manning scores with changes in QOL domains

Manning symptoms also showed a significant negative correlation across all four sub-domains of the questionnaire. The greatest effect was seen in the GI symptoms domain, with a 3.9% (***-2.98 ± 0.66 p<0.001***) lower domain score for each symptom present. The other sub-domains showed a similar negative effect, but the measured effect on global QOL was less. Figures are summarised in Table 14 below.

QOL Domain	Change in Domain Score for Each Manning Symptom Recorded	Std. Error	% Change in Global Score	% Change in Domain Score	P Value
GI symptoms	-2.98	0.66	-2.1%	-3.9%	<0.001
Physical	-1.30	0.34	-0.9%	-4.6%	<0.001
Social	-0.59	0.22	-0.4%	-2.9%	<0.001
Emotions	-0.72	0.24	-0.5%	-3.6%	<0.001

Table 14. *The effect of Manning symptoms on GIQLI sub domain scores after surgery*

8.4.2 Manning symptoms as predictors of outcome

The six individual symptoms that make up the Manning criteria (Table 1) were examined to see if any were predictors of outcome. Three out of the six were found to be significant. The largest effect was seen in patients who described loose bowel movement with the onset of pain. Regression analysis showed that patients with this symptom had a ***-17.3 ± 4.6 (p<0.001)*** lower global QOL score following surgery compared to those who didn't (Table 15). Abdominal distension was the most frequently described symptom (Figure 11.) but was not a significant predictor of outcome.

Manning Symptom	Mean Change in QOL	Std. Error	% Change in Global Score	P Value
Loose Bowel Movement with Pain	-17.3	4.6	-11.9%	<0.001
More Frequent Bowel Movement with Pain	-14.9	5.4	-10.3%	0.007
Pain Relief with Bowel Movement	-14.1	5.3	-9.8%	0.009
Abdominal Distension	-6.9	4.1	-4.8%	NS
Passage of Mucous	-11.1	5.9	-7.7%	NS
Incomplete Emptying	-11.4	5.7	-7.9%	NS

Table 15. *The effect of the individual Manning symptoms on QOL*

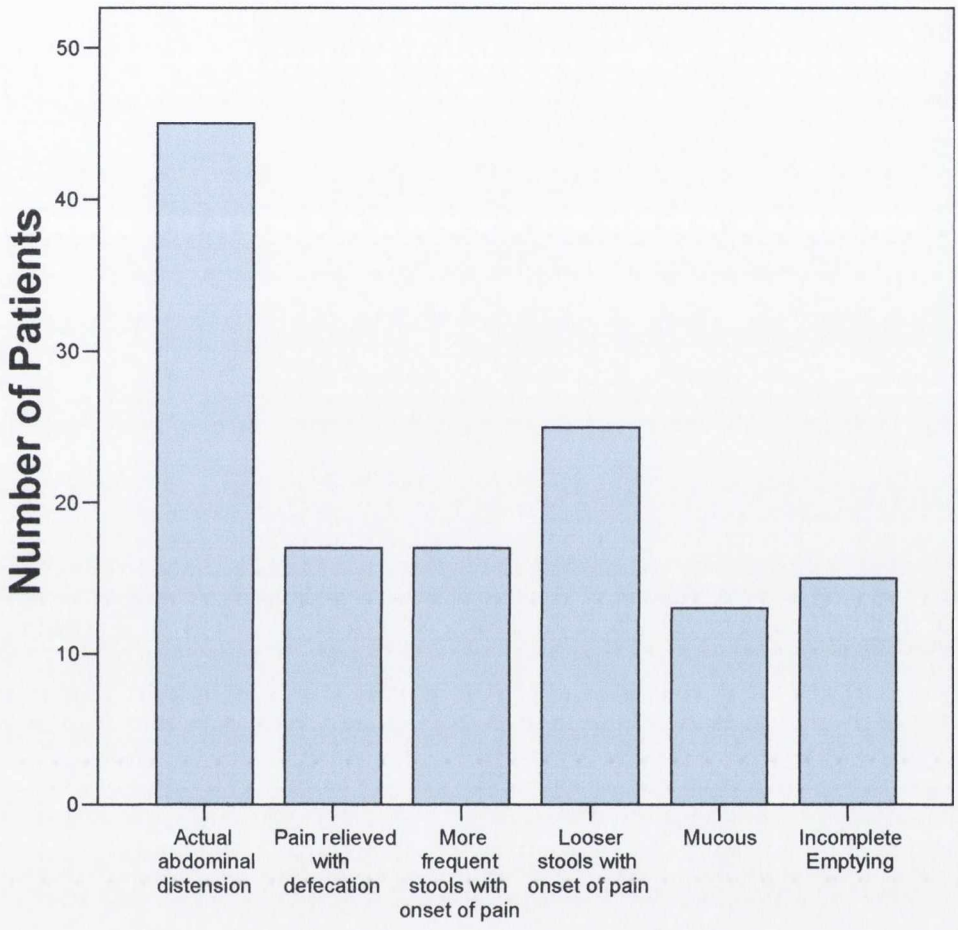


Figure 11. Frequency of Manning Symptoms Recorded

8.5 Comparison of Rome scores with change in QOL

Rome scores also showed a significant negative correlation with QOL change following surgery. As we have discussed, the Rome II criteria (Table 3) are a subdivision of the Manning criteria with an added chronicity term. Of the 32 patients with 2 or more Manning symptoms present, 21 (19%) also fulfilled the Rome II criteria for diagnosis of IBS and had a ***-12.5 ± 5.0 (p=0.15)*** lower QOL after surgery compared to those who didn't. When the Rome II criteria were compared to the changes in domain scores, they had a significant negative effect on the GI symptoms and physical function sub-domains but not the social or emotional domains (Table 16).

QOL Domain	Change in Domain Score for Each Rome Symptom Recorded	Std. Error	% Change in Global Score	% Change in Domain Score	P Value
GI symptoms	-7.41	2.61	-5.1%	-9.7%	0.005
Physical	-3.54	1.31	-2.5%	-12.6%	0.008
Social	0.55	0.77	+0.4%	+2.8%	NS
Emotions	0.65	0.08	+0.5%	+3.2%	NS

Table 16. *The effect of the Rome II criteria on GIQLI sub domain scores after surgery*

8.6 Comparison of functional GI symptoms with change in QOL

The functional gastrointestinal symptoms recorded in the pro-forma (Appendix 5) including nausea and vomiting were correlated with change in QOL after surgery. A feeling of fullness was the only one found to be a significant predictor of outcome. There was an ***11.1 ± 5.2 (p=0.035)*** higher QOL score in patients describing this symptom. Results of outcome are summarised below (Table 17), and frequencies in Figure 12.

Manning Symptom	Mean Change in QOL	Std. Error	% Change in Global Score	P Value
Feeling of Fullness	+11.1	5.2	+7.7%	<0.001
Bloating/Tightness	+0.2	4.3	+0.1%	NS
Heartburn	-7.9	4.8	-5.5%	NS
Dysphagia	-1.6	11.1	-1.1%	NS
Early Satiety	-2.4	4.8	-1.6%	NS
Belching	-6.0	4.6	-4.2%	NS
Nausea and Vomiting	-4.4	5.5	-3.1%	NS

Table 17. *The effect of functional gastrointestinal symptoms on QOL*

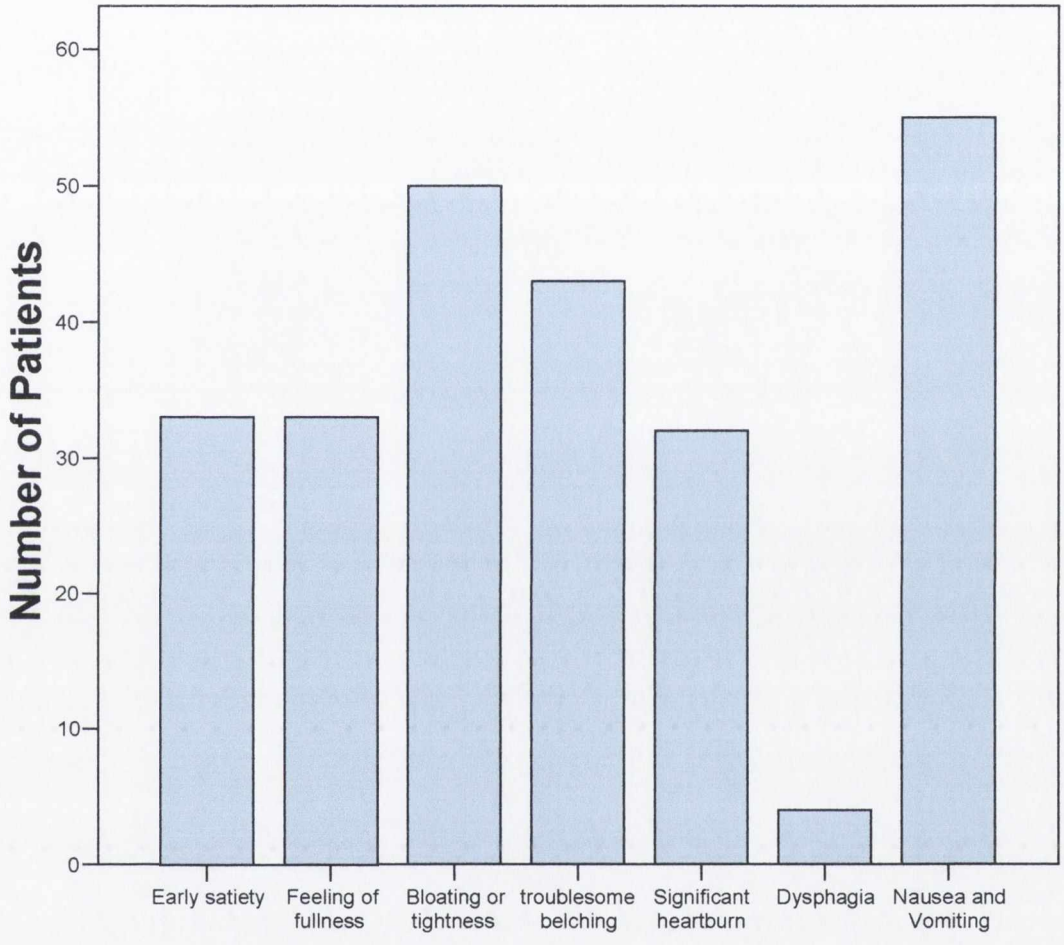


Figure 12. Frequency of Functional GI Symptoms

8.7 Cholelithiasis and change in QOL

The three variables specific to cholelithiasis were correlated with change in QOL and none were found to be significant predictors of outcome (Table 18).

Manning Symptom	Mean Change in QOL	Std. Error	% Change in Global Score	P Value
Previous Abnormal Liver Function Tests	+2.0	5.2	+1.4%	NS
Fat Intolerance	+5.8	4.3	+4.0%	NS
Previous Gallstone Related Complication	+3.3	4.8	+2.3%	NS

Table 18. *The effect of symptoms of cholelithiasis on QOL*

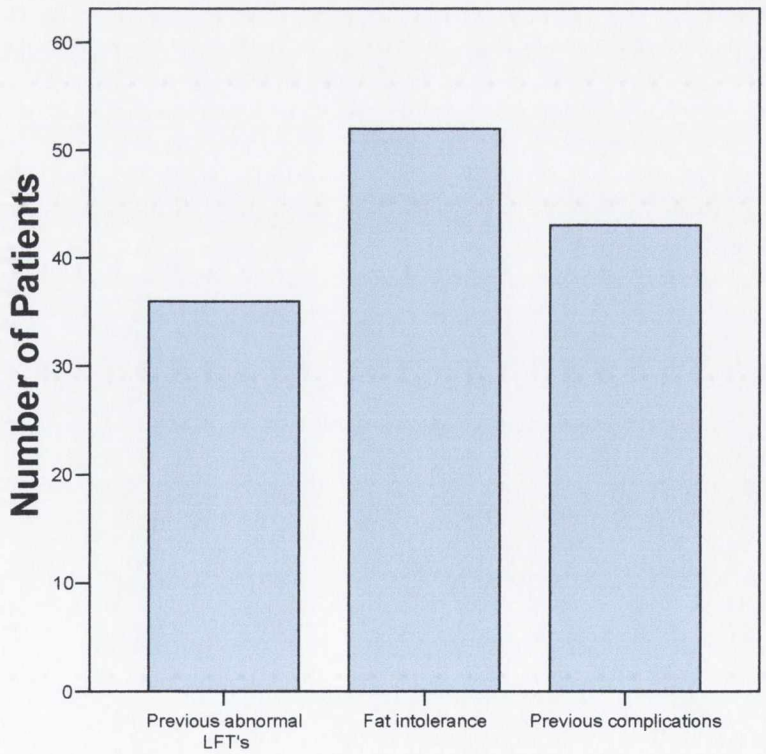


Figure 13. Frequencies of Gallstone Related Variables

8.8 Psychiatric history

A previous psychiatric history was recorded in 19 patients (17%). All were female with 15 describing an ongoing or previous depressive illness, and the remaining 4 having anxiety related disease. In terms of outcome this was highly significant with a ***-21.5 ± 5.2 (p<0.001)*** lower QOL score after surgery compared to those without a psychiatric history. 12 of the 19 (63%) had 2 or more Manning symptoms present.

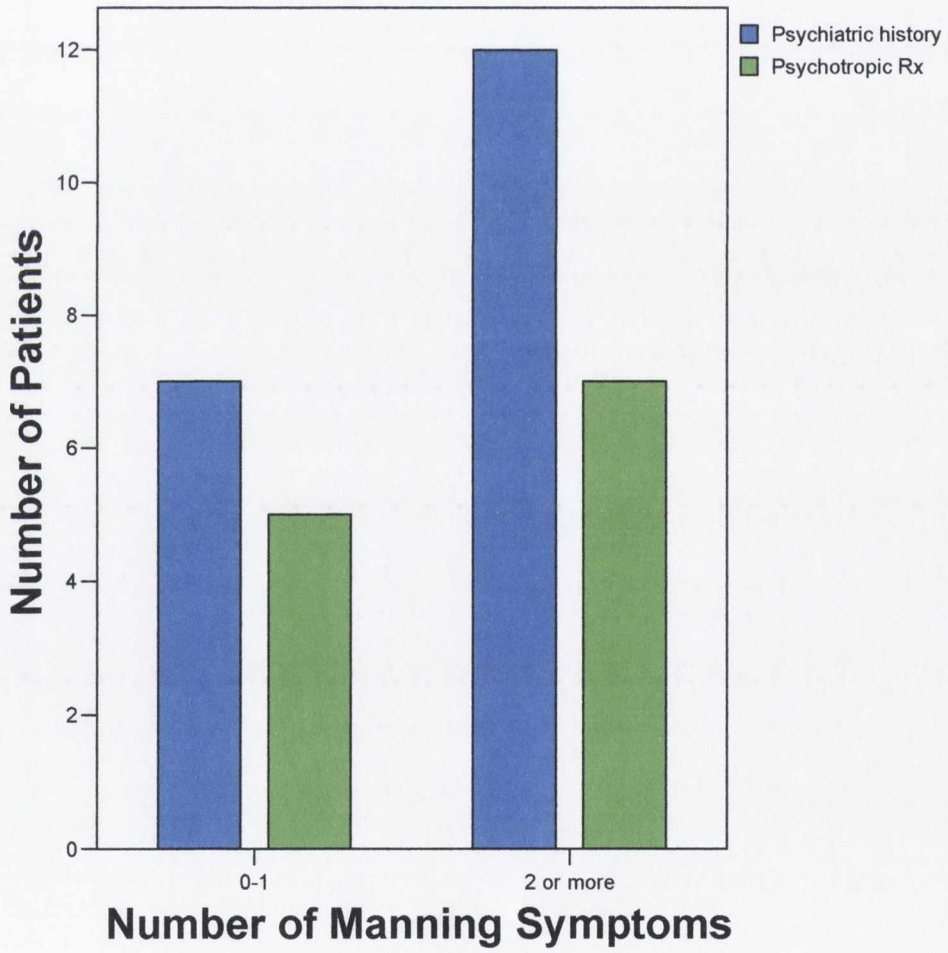


Figure 14. Psychiatric History & Treatment vs. Manning Symptoms

Chapter 9

Discussion

9.1 Introduction

The present study was designed to investigate the correlation between preoperative symptoms of FGID's (i.e. IBS) and outcome following laparoscopic cholecystectomy for symptomatic gallstones. The primary outcome measurement was QOL using the GIQLI. The hypothesis stated that "Patients undergoing laparoscopic cholecystectomy for gallstones do not experience significant quality of life improvement, if they exhibit typical features of irritable bowel syndrome".

Postcholecystectomy syndrome is a term used to encompass a diverse variety of symptoms that can persist following surgery for gallstones. The quoted relief rates vary from 65 to 95% (Bates *et al.*, 1991; Luman *et al.*, 1996), and there is evidence to show that the surgical technique employed (i.e. open or laparoscopic) does not influence long term outcome (Peterli *et al.*, 2000). In a recent meta- analysis Berger *et al* (Berger *et al.*, 2003) showed that patients exhibiting typical biliary pain had higher relief rates than those who's main complaint was dyspepsia (92% vs. 46 to 89% respectively).

There are undoubtedly patients whose predominant symptoms are functional, yet have surgery for gallstones. Luman *et al* (Luman *et al.*, 1996) warned against

operating on those who experienced bloating and altered bowel habit and required psychotropic medication. They stated that these types of patients were unlikely to benefit from surgery, and would be expected to have a higher rate of persistent symptoms after cholecystectomy. IBS is one of the functional gastrointestinal disorders characterised by abdominal discomfort along with altered defaecation or change in bowel habit. The symptoms of IBS commonly overlap those of functional dyspepsia (Talley *et al.*, 1999), and in patients with coexistent gallstones drawing up a management plan can be difficult. IBS sufferers are a group that one might expect to have a less favourable result following surgery for gallstones. No previous study has shown a worse outcome after cholecystectomy in this subgroup. Evidence that surgery could be avoided in some IBS patients is supported by population based studies showing higher cholecystectomy rates compared to the general population (Fielding, 1977; Kennedy and Jones, 2000). On the other hand this increased rate of intervention may indeed be appropriate. It could be explained by altered colonic motility predisposing IBS patients to gallstone formation (van Erpecum and van Berge-Henegouwen, 1999) or by an underlying neuro-physiological condition affecting smooth muscle contractility in both the gastrointestinal and biliary systems and causing symptoms in both these organ systems (Kellow *et al.*, 1999).

Nevertheless there is clear evidence that in the laparoscopic era the rate of cholecystectomy has increased without a parallel increase in the prevalence of gallstones. One Scottish group reported an increased surgery rate of up to 25% between 1989 and 1993 (Lam *et al.*, 1996). Numerous studies have shown distinct advantages over its open counterpart (Grace *et al.*, 1991; Macintyre and Wilson, 1993), and with reduced risk-benefit ratios this higher surgical rate may reflect a

lower threshold for intervention or a higher demand for 'key hole' surgery by patients. With over 50,000 laparoscopic cholecystectomies preformed in the UK and Ireland each year, this has major cost implications. If we could predict patients who were less likely to benefit from surgery and treat them expectantly, there would be financial gains and benefits in terms of patient health from reduced morbidity by unnecessary surgery.

9.2 Summary of results and discussion

9.2.1 Recruited patients

From the one hundred and fifty eight patients initially recruited to the study thirty five (22.2%) failed to complete at least one of the postoperative questionnaires. Data from these patients could not be included in the study. This matched the expected drop out rate predicted at the time of the power calculation, and was similar to other studies where follow-up by postal survey has been utilised (Kennedy and Jones, 2000; Quintana *et al.*, 2003a). 111 (99.1% of included subjects) completed the 6 week questionnaire (Q2), 73 (65.2% of included subjects) completed the 3 month questionnaire (Q3) and 64 (57.2% of included subjects) completed the 2 year questionnaire (Q4). This reduction in 35 patients between Q1 and Q2 and 38 between Q2 and Q3 highlights how compliance is affected by this method of administration. To encourage patients to return the questionnaire we used stamped addressed envelopes and we contacted patients on a second occasion if they had not replied within a given time frame. It was felt to be unethical to pursue follow-up any further after patients failed to reply to the reminder letter. Compliance might have increased

if we had contacted patients by phone and administered the questionnaire orally. However, this would have introduced unnecessary bias into the study. Despite the drop out rate over the two year period, a statistically significant change in QOL after surgery was still measured at all 3 time points (Table 4 & 5).

9.2.2 Quality of life after surgery

Global quality of life scores changed significantly following laparoscopic cholecystectomy. This supports previous publication that the GIQLI has sufficient responsiveness to detect changes in health status after surgery for cholelithiasis (Eypasch *et al.*, 1995; Mentes *et al.*, 2001; Quintana *et al.*, 2003a), and suggests that the decision to use the GIQLI instrument in the study was correct. The results provide further validation data of the index and for its use in patients with gallstone disease.

Following surgery there was a significant improvement in QOL at the Q2 time point and there continued to be slight improvement until Q3 although there was no significant difference between the two ***1.7 ± 2.2 (p=0.423)***. The mean improvement of Q2 and Q3 was ***+17.6 points (12.2%)***. This was higher than the 5 to 10% some authors quote as being a significant change in QOL noticeable to patients (Osoba, 2002), and interestingly is the same value quoted for QOL improvements after laparoscopic cholecystectomy in the original validation paper for the index (Eypasch *et al.*, 1995). At Q4 there was a significant regression towards the baseline of ***-7.6 ± 2.3 (p=0.003)*** with the mean change in QOL from preoperative levels of ***+10.8 points (7.5%)***. The majority of published studies examining QOL after laparoscopic cholecystectomy have a short follow-up of only 3 to 6 months (Eypasch *et al.*, 1995;

Mentes *et al.*, 2001; Quintana *et al.*, 2003a). There is limited data available on long term outcome and on whether QOL changes are sustained. Only two papers publish long term data (Topcu *et al.*, 2003; Vetrhus *et al.*, 2004), neither of which showed a similar pattern of regression seen in this study. As previously discussed both these publications are flawed, the Topcu paper for not presenting preoperative QOL data and the Vetrhus paper for using an instrument unlikely to be responsive enough to detect a significant change.

There are several possible explanations for the regression measured at 2 years. Firstly, there could be an initial placebo affect afforded by the surgical intervention, with subsequent return of symptoms. There is already published data showing significant placebo responses of near 70% in patients with functional dyspepsia (Talley *et al.*, 1991), and as can be seen in Figures 11 & 12 a large proportion of study patients described these types of symptoms. The Hawthorne effect is similar to the placebo effect and could also partly explain these differences (Braunholtz *et al.*, 2001). It describes changes in patient or clinical behaviour as a result of involvement in clinical trials. It is due to increased knowledge or interest in the study or due to the patients feeling of being observed. Secondly, the regression may in part be caused by complications or side effects of the surgery itself. Laparoscopic cholecystectomy is a minimally invasive procedure, but there will undoubtedly be some degree of adhesion formation within the peritoneal cavity which may be symptomatic. This, however, is unlikely to be cause a regression at 2 years, as adhesions form shortly after surgery and are more likely to present earlier. There has also been a reported increase in diarrhoea following cholecystectomy that may be persistent (Hearing *et al.*, 1999; Sauter *et al.*, 2002). This may not be apparent at the 3 month time point, but might

significantly affect QOL when measured at 2 years. As discussed below the GI sub domain of the questionnaire did not regress at 2 years and therefore would not support this assumption. Thirdly, it is possible that at two years patients who remain asymptomatic are less likely to return the final questionnaire. This would leave a higher proportion of patients having a worse outcome, resulting in a negative effect on the mean QOL at Q4. We know that patients with postcholecystectomy syndrome have higher anxiety levels and that the pathogenesis may form part of a somatisation disorder (Stefaniak *et al.*, 2004). This type of patient may be more likely to ruminate on symptoms, actively seek medical help and subsequently complete the questionnaire. Since IBS is closely related to anxiety and abnormal health seeking behaviour we might expect a higher percentage of IBS sufferers to complete Q4. Again this assumption is not supported by Figures from this study. 28% of patients who returned Q2 had 2 or more Manning symptoms compared to 25% who returned Q4, so one might assume this is a true regression in QOL. Lastly, the regression may be due to exacerbation of symptoms unrelated to biliary disease, but related to some underlying problem such as dyskinesis.

9.2.3 QOL change and domain scores

The four sub-domains of the questionnaire changed in a similar fashion to the global score. There was an initial large improvement at Q2 and a smaller but non significant increase at Q3 (Tables 6 to 13 and Figures 8 & 9). There was however differences observed between Q3 and Q4 for the 4 domains. The improvement observed in the GI symptoms domain was maintained to the end of the study period ***57.1 ± 1.1 ($p<0.001$)***. This domain contained symptoms such as abdominal pain,

change in bowel habit, symptoms of dyspepsia and questions related to eating (Appendix 2), all of which are important when considering FGID's and postcholecystectomy syndrome. As mentioned above this domain does not account for the regression in global score between Q3 and Q4, so side effects of cholecystectomy are unlikely to be the explanation for this change. Similarly the emotions sub domain had a sustained improvement at Q4 ***14.1 ± 0.4 (p<0.001)***. This domain looks at how patients feel about their illness and how they cope with everyday stress. It would appear that laparoscopic cholecystectomy affords significant improvement in this area. The remaining two sub-domains showed regression from Q3 to Q4. The physical domain showed partial regression ***-1.8 ± 0.72 (p=0.012)*** and the social domain full regression back to baseline ***-3.1 ± 0.5 (p<0.001)***. These domains seem to account for the decline in global QOL score observed at two years, and suggest that after initial improvement patients find problems with physical strength, energy levels and ability to perform normal activities. With no change in the GI symptoms domain, this does not appear to relate to recurrent or persistent symptoms. It is possible that outside factors such as personal problems, economic constraints or social support are influencing these domains (King and Napa, 1998; Klose, 2003). It is not possible to give a definitive reason for these differences.

9.2.4 Influence of Manning symptoms on QOL

One of the aims of this prospective study was to show that patients with IBS did not experience a significant QOL improvement after surgery. The Manning criteria (Table 1) are a set of 6 symptoms used to aid the diagnosis of IBS and they were one of the measurements used in the preoperative assessment of the study group.

At recruitment 32 patients (28.8%) had two or more of the Manning symptoms present, with this percentage maintained in the patients who replied to subsequent follow-up. Figure 6 shows that approximately 20% of patients remain unchanged or have a measured reduction in QOL after surgery. When this group was considered in isolation, they were found to have ***1.95 ± 0.39 (p=0.037)*** times the number of Manning symptoms compared to the 80% that improved. This goes some way to support the hypothesis that patients with IBS do not experience significant QOL improvements after laparoscopic cholecystectomy, and was further corroborated, when Manning symptoms were correlated with change in QOL after surgery for the study group as a whole (Figure 10). Using regression analysis with the mean postoperative QOL score as the dependent variable and the mean global score of Q1 along with Manning symptoms as independent variables there was a ***5.2 ± 1.29 (p<0.001)*** lower score for every Manning symptom that was present. This means that, patients exhibiting three Manning symptoms would be expected to have a global QOL score on the GIQLI of around 15 points lower than those who had none. In Figure 10, the mean change in QOL is measured along the Y axis, with the red line at zero representing no change in QOL. The X axis represents an increasing number of Manning symptoms that patients described preoperatively. It can be clearly seen that the mean change in QOL reduces towards zero with an increasing number of Manning symptoms, and we would expect those patients describing 5 or more of the Manning symptoms preoperatively to have no improvement in QOL score after surgery.

From these data it is easy to understand why patients with IBS did not have an increase in the QOL score after surgery, but as mentioned earlier a significant proportion of patients actually regressed from baseline and had a lower QOL which

needs some explanation. Firstly, QOL is a dynamic variable (Bergner, 1989; Olschewski *et al.*, 1994), meaning scores will vary from day to day or even hour to hour. The recorded negative effect could have simply been a variation of the normal QOL experienced by patients who had no improvement after surgery. Secondly, the reduced score could also be as a result of an unrealistic expectation from the surgical procedure. The results have already shown that patients with IBS have a significantly worse outcome after surgery. If these patients had high expectations that intervention would cure their symptoms, yet experience little or no benefit from the procedure, focusing on persistent complaints may have had a negative effect on outcome. In clinical practice it is not uncommon to see patients returning after surgery claiming to be worse than ever. I do not have data to support these hypotheses, so a definitive answer is outside the scope of these results.

Manning symptoms also had a significant negative effect on all four sub-domains of the questionnaire (Table 14). Unsurprisingly, the largest measured effect on global QOL (-2.1% for each Manning symptom present) was from the GI symptoms domain, which showed a ***-2.98 ± 0.66 $p<0.001$*** lower domain score for each Manning symptom present. With the majority of the Manning symptoms being directly measured in this section of the questionnaire and with this domain contributing to over 50% of the final score, it was probable that this pattern would be observed.

9.2.5 Influence of preoperative symptoms on QOL

The second aim of this study was to preoperatively identify a group of patients unlikely to benefit from intervention. To do this, groups of symptoms were correlated with change in QOL using regression analysis in order to predict outcome. The 6 individual Manning symptoms (Table 15), functional GI symptoms (Table 17), variables specific to cholelithiasis (Table 18) and psychiatric history (Figure 14) were all examined.

Three of the Manning symptoms were shown to be significant predictors of outcome; they were loose bowel movement with onset of pain ***-17.3 ± 4.6 (p<0.001)***, more frequent bowel movement with onset of pain ***-14.9 ± 5.4 (p=0.007)*** and pain relief with defaecation ***-14.1 ± 5.3 (p=0.009)***. The most frequently described Manning symptom was abdominal distension. It was recorded in 45 patients (Figure 11) but despite a negative effect on outcome it was not shown to have a significant predictive value. Interestingly, the three Manning symptoms shown to be significant are the three that make up the Rome II criteria. In a similar way to the Manning criteria, the 21 patients who fulfilled the Rome II criteria had a negative correlation with QOL outcome ***-12.5 ± 5.0 (p=0.15)***. The lower number of IBS patients identified with the Rome II criteria corroborates the findings of Saito (Saito *et al.*, 2000) and our results suggest that the Manning criteria are perhaps more sensitive and the Rome II criteria more specific at identifying patients with IBS.

Functional GI symptoms were a common finding in the group (Table 17), with almost 50% of patients complaining of bloating or troublesome wind. Unlike the Manning or Rome symptoms however they were poor at predicting patient outcome.

A feeling of fullness was the only significant symptom recorded, and was in fact the only one found to have a significant predictive value for better outcome after laparoscopic cholecystectomy ***+11.1 ± 5.2 (p<0.001)***. One possible explanation was poor patient understanding or interpretation of symptoms, which are often vague or intermittent. Even for clinicians the classification of functional dyspepsia has been confusing in the past (Talley *et al.*, 1991), until more recently when a multinational working group clearly defined diagnostic subgroups and symptoms (Talley *et al.*, 1999). During questioning it was common for patients to confuse symptoms, for example, early satiety with anorexia, or tightness and bloating with abdominal distension. Despite these being explained during patient assessment, it does raise doubts as to the accuracy with which these symptoms were recorded. On the other hand these symptoms may be an equally common finding in both patients suffering predominantly from gallstones or in those whose primary complaint is functional dyspepsia. In terms of QOL, outcome would then be variable. This is supported by previous publications stating that relief of functional symptoms following laparoscopic cholecystectomy is unpredictable (Bates *et al.*, 1991; Luman *et al.*, 1996; Peterli *et al.*, 2000). In any case, it may have been useful to record these symptoms again after surgery, which perhaps could have helped us gain a better understanding of the observed changes.

Surprisingly, the three variables specific to cholelithiasis were of no predictive value for QOL outcome (Table 18). They all showed a slight increase in mean QOL scores after surgery, but these changes were not significant. Of the 45 patients that had previous complications from gallstones, 21 had cholecystitis, 11 pancreatitis, 11 jaundice and 2 cholangitis. It's difficult to explain why we couldn't correlate

significant QOL improvements in this group. In most cases complications were a significant time before surgery and perhaps had no affect on baseline QOL at the time of interview. Fatty food intolerance is classically described in textbooks as a feature of gallstones and for this reason was included in this section. Despite a 5.8 higher QOL for patients describing this symptom, there was no significant correlation with outcome. This corroborates findings of previous studies that show a weak relationship between this symptom and gallstones (Berger *et al.*, 2003). Some studies have shown only transient improvement of this symptom after surgery explained by the placebo effect of operation (Ure *et al.*, 1995).

Lastly, the effect of a previous or ongoing psychiatric history was examined. It had a highly significant effect on outcome with a ***-21.5 ± 5.2 ($p<0.001$)*** lower QOL score when present. This correlates well with previous studies that have shown that patients with postcholecystectomy syndrome have a higher incidence of anxiety (Markert, 1991) and depression (McMahon *et al.*, 1995) and a higher use of psychotropic medications (Luman *et al.*, 1996). There is also a strong association between IBS and anxiety disorders (Talley and Spiller, 2002). The results showed an almost twofold higher psychiatric history in those patients with two or more Manning symptoms (Figure 14).

In summary I have been able to show that patients with IBS have a significantly worse outcome after laparoscopic cholecystectomy for gallstones. I have also been able to demonstrate several symptoms that when present preoperatively, have a significant predictive value for poor QOL outcome. Based on these findings patients likely to have a less favourable outcome could be identified before having

surgery. This does not justify a blanket statement for avoiding cholecystectomy in patients with IBS. This would require a randomised controlled trial comparing treatments along with assessment of outcome in terms of complication rates from gallstones, morbidity and mortality. It does, however, give an opportunity to assess what expectations a patient has for surgery and counsel them appropriately. In patients with asymptomatic gallstones, complications such as jaundice, pancreatitis and cholecystitis are almost always preceded by symptoms (Thistle *et al.*, 1984; Friedman *et al.*, 1989). There is supporting evidence that gallstones have a relatively benign natural history and with an onset of symptoms of approximately 1-4% per year, many of these patients can be safely treated expectantly (Ransohoff *et al.*, 1983; Friedman, 1993; Attili *et al.*, 1995b). In patients with IBS, we would recommend that each case be evaluated on its own merit, with careful consideration of risk factors, potential complications from gallstones managed non-operatively and on the patients own wishes.

9.3 Critical assessment

9.3.1 Patient compliance

For the power calculation a 30% drop out rate was predicted based on previous mail surveys. At Q2 the drop out rate was actually slightly less than this at 22%; however patients failed to respond in similar proportions between Q2 and Q3 and again between Q3 and Q4. The final 64 patients who completed Q4 represented 57% of those included in the final study analysis, but only 42% of the total initially recruited.

More could have been done to improve the compliance of the study group. Firstly patients could have been contacted by telephone (their contact number was recorded in the initial pro-forma) to ensure the questionnaire had been received or to complete the questionnaire over the phone. The latter may have introduced unnecessary bias to the results. Secondly, arrangements could have been made to hand deliver questionnaires and complete them in person, or strict outpatient appointments could have been made for all those recruited to the study. Both these options would have been considerably labour intensive, and the first has ethical issues as patients may have felt obliged to answer the questionnaire when they did not want to. Despite the relatively poor patient compliance we still showed significant changes in postoperative QOL, which correlated well with symptoms of IBS.

9.3.2 Post operative symptoms

It would have been beneficial to repeat the patient pro-forma (Appendix 5) after the 2 year follow-up or at each subsequent visit, and record postoperative symptoms. This is a fair criticism of the study given that it may have added significantly to our understanding and interpretation of the data.

9.4 Conclusions

This study concludes that:

- A significant proportion of patients with gallstones experience measurable and sustained QOL improvements following laparoscopic cholecystectomy.

- The GIQLI shows sufficient responsiveness to be used as a tool for measuring QOL outcome in patients with cholelithiasis.

- Patients with symptoms of IBS indicated by the Manning criteria show significantly less improvement in QOL following laparoscopic cholecystectomy for gallstones.

- The symptoms of loose bowel movement with onset of pain, more frequent bowel movement with onset of pain, pain relief with defaecation and a previous psychiatric history were significant predictors of poor outcome in terms of QOL improvement after laparoscopic cholecystectomy.

These results emphasise that through simple history taking and patient evaluation, we can identify individuals likely to have a less favourable outcome after laparoscopic cholecystectomy, thus giving us the opportunity to counsel them appropriately.

9.5 Future directions

This is the first QOL study to show that patients with IBS have a significantly worse outcome following laparoscopic cholecystectomy for gallstones. Further research should be done to confirm these findings, and to examine treatment options for this group of patients. Suggested areas of research include:

1. A larger randomised controlled trial in patients with IBS and gallstones comparing QOL outcome after laparoscopic cholecystectomy to other non surgical management strategies.

2. Objective parameters of gallbladder disease such as histological changes within the gallbladder specimens or preoperative USS findings could be compared with QOL improvement following laparoscopic cholecystectomy in patients with IBS which might help corroborate our findings.

3. More work should be done at assessing our ability as clinicians to predict patients likely to have poor QOL outcome following laparoscopic cholecystectomy. Measures could be taken to introduce and validate a scoring method to help in this process.

4. It is clear that there is a lack of good QOL research in the field of HPB surgery. There are many aspects of both benign and malignant disease that have not yet been examined. Presently, there is no universally accepted or validated questionnaire specific to this field. It would be beneficial to construct, publish and validate such a questionnaire.

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Author (ref.)	Year	Study aim	QOL index	No.	Design criticisms	Findings
Plaisier (Plaisier *et al.*, 1994)	1994	ESWL vs. open surgery	NHP	49	Unresponsive questionnaire and small numbers	Significant improvement in QOL in open surgery compared with ESWL
Plaisier (Plaisier *et al.*, 1995)	1995	QOL in laparoscopic vs. open surgery	NHP	31	Unresponsive questionnaire and not randomised/small numbers	Significant QOL improvement in both the laparoscopic and the open group (earlier in the laparoscopic group)
Mentes (Mentes *et al.*, 2001)	2001	QOL in symptomatic and asymptomatic gallstones after surgery	GIQLI	62	Short follow-up of only 4 months	Significant QOL improvement in both groups
Carrilho – Ribeiro (Carrilho-Ribeiro *et al.*, 2002)	2002	Successful ESWL vs. unsuccessful ESWL	GIQLI	36	Single QOL measurement/ telephone interview and small numbers	No significant difference in scores
Boerma (Boerma *et al.*, 2002)	2002	Wait-and-see vs. cholecystectomy after sphincterotomy	SF-24 (controls SF-36)	108	No preoperative measurement / inappropriate questionnaires for study group and controls	No significant difference in QOL between groups – QOL unhelpful for selection
Topcu (Topcu *et al.*, 2003)	2003	QOL after laparoscopic and open cholecystectomy	SF-36 & part of GIQLI	200	No randomisation / No preoperative QOL measurement and non validated part of GIQLI	Significant improvement in all 8 sub domains of the SF-36 in favour of laparoscopic cholecystectomy
Lorusso (Lorusso *et al.*, 2003)	2003	Influence of psychological features on QOL after surgery	SCR-90-R & GSRS	58	None	Those with gallstones and dyspepsia are unlikely to benefit from cholecystectomy if they show psychological features
Quintana (Quintana *et al.*, 2003)	2003	Clinical factors that predict outcome after cholecystectomy	SF-36 & GIQLI	698	Failed to publish indications for surgery in the asymptomatic high risk group	Largest QOL gains seen in the low risk symptomatic group
Vetrhus (Vetrhus *et al.*, 2004)	2004	QOL in laparoscopic cholecystectomy vs. observation	NHP PGWB VAS	137	? Incorrect choice of questionnaires	Unexpectedly found significant improvement in QOL at 6 months in both groups

Appendix 1: Table showing QOL publications relating to gallstones

The Gastrointestinal Quality of Life Index (GIQLI)

Demographic details to be filled in by doctor :-

Name:
Address:

D.O.B.

Date:

Questionnaire:

☐ ☐ ☐ ☐

Q1 *Q2* *Q3* *Q4*

Please circle the most appropriate answer to *ALL* of the 36 questions

1) How often during the past 2 weeks have you had pain in the abdomen?

All of the time , most of the time , some of the time , a little of the time , never

2) How often during the past 2 weeks have you had a feeling of fullness in the upper abdomen?

All of the time, most of the time , some of the time , a little of the time , never

3) How often in the past 2 weeks have you had bloating (sensation of too much gas in the abdomen)?

All of the time, most of the time , some of the time , a little of the time , never

4) How often during the past 2 weeks have you been troubled with excessive passage of gas through the anus?

All of the time, most of the time , some of the time , a little of the time , never

5) How often during the past 2 weeks have you been troubled by strong burping or belching?

All of the time, most of the time , some of the time , a little of the time , never

6) How often during the past 2 weeks have you been troubled by gurgling noises from the abdomen?

All of the time, most of the time , some of the time , a little of the time , never

7) How often during the past 2 weeks have you been troubled by frequent bowel movements?

All of the time, most of the time , some of the time , a little of the time , never

8) How often during the past 2 weeks have you found eating a pleasure?

All of the time, most of the time , some of the time , a little of the time , never

9) Because of your illness, to what extent have you restricted the kind of food you eat?

Very much , much , somewhat , a little , not at all

10) During the past 2 weeks, how well have you been able to cope with everyday stress?

Extremely poorly , poorly , moderately , well , extremely well

11) How often during the past 2 weeks have you been sad about being ill?

All of the time, most of the time , some of the time , a little of the time , never

12) How often during the past 2 weeks have you been nervous or anxious about your illness?

All of the time, most of the time , some of the time , a little of the time , never

13) How often during the past 2 weeks have you been happy with life in general?

Never , a little of the time , some of the time , most of the time , all of the time

14) How often during the past 2 weeks have you been frustrated with your illness?

All of the time, most of the time , some of the time , a little of the time , never

15) How often during the past 2 weeks have you been tired or fatigued?

All of the time, most of the time , some of the time , a little of the time , never

16) How often during the past 2 weeks have you felt unwell?

All of the time, most of the time , some of the time , a little of the time , never

17) Over the past 2 week, have you woken up in the night?

Every night , 5-6nights , 3-4nights , 1-2nights , never

18) Since becoming ill have you been troubled by changes in your appearance?

A great deal , a moderate amount , somewhat , a little bit , not at all

19) Because of your illness how much physical strength have you lost?

A great deal , a moderate amount , some , a little bit , none

20) Because of your illness, to what extent have you lost your endurance?

A great deal , a moderate amount , somewhat , a little bit , not at all

21) Because of your illness, to what extent do you feel unfit?

Extremely unfit , moderately unfit , somewhat unfit , a little unfit , fit

22) During the past 2 weeks, how often have you been able to complete your normal daily activities (school , work , household etc..)?

All of the time, most of the time, some of the time , a little of the time , never

23) During the past 2 weeks, how often have you been able to take part in your usual patterns of leisure or recreational activities?

All of the time, most of the time , some of the time , a little of the time , never

24) During the past 2 weeks, how much have you been troubled by the medical treatment of your illness?

Very much , much , somewhat , a little , not at all

25) To what extent have your personal relations with people close to you (family and friends) worsened because of your illness?

Very much , much , somewhat , a little , not at all

26) To what extent has your sexual life been impaired (harmed) because of your illness?

Very much , much , somewhat , a little , not at all

27) How often during the past 2 weeks, have you been troubled by fluid or food coming back up into your mouth (regurgitation)?

All of the time, most of the time , some of the time , a little of the time , never

28) How often during the past 2 weeks have you felt uncomfortable because of your slow speed of eating?

All of the time, most of the time , some of the time , a little of the time , never

29) How often during the past 2 weeks have you had trouble swallowing your food?

All of the time, most of the time , some of the time , a little of the time , never

30) How often during the past 2 weeks have you been troubled by urgent bowel motions?

All of the time, most of the time , some of the time , a little of the time , never

31) How often during the past 2 weeks have you been troubled by diarrhoea?

All of the time, most of the time , some of the time , a little of the time , never

32) How often during the past 2 weeks have you been trouble by constipation?

All of the time, most of the time , some of the time , a little of the time , never

33) How often during the past 2 weeks have you been troubled by nausea?

All of the time, most of the time , some of the time , a little of the time , never

34) How often during the past 2 weeks have you been troubled by blood in the stools?

All of the time, most of the time , some of the time , a little of the time , never

35) How often during the past 2 weeks have you been troubled by heartburn?

All of the time, most of the time , some of the time , a little of the time , never

36) How often during the past 2 weeks have you been troubled by uncontrolled stools?

All of the time, most of the time , some of the time , a little of the time , never

Appendix 2: The Gastrointestinal Quality of Life Index

Verbal Consent Form

Title: Quality of life measurement following laparoscopic cholecystectomy

You are invited to take part as a volunteer in the above research study. You are free to decline to participate without giving a reason. If you decide not to take part, your decision will be accepted without question or displeasure and you will be treated as though the matter had not arisen, without disadvantage to your future care.

If you do agree to participate in the study, you are free to withdraw at any time, without giving reason or explanation. Withdrawal will be accepted without question or displeasure and without any disadvantage to your future care.

As part of the research study you will be asked to complete four short questionnaires, which focus on aspects of your illness and its impact on your daily activities. The gallbladder specimen removed at the time of surgery will also be examined at the regional pathology department at the Royal Victoria Hospital.

Information gathered during the course of the study will remain confidential, and no publications or reports generated from the study will identify you as an individual.

NAME OF PATIENT _____

ADDRESS _____

_____

_____

_____

Please read the *patient information sheet* provided before you give consent to take part in this study.

Research Co-ordinator

I have explained the nature and purpose of the study to the above subject and he/she has freely given consent

Signed _____(research co-ordinator) Date _____

Name (print) _____

Witnessed verbal consent:

The above named patient has given verbal consent to participate in the above study in accordance with the terms outlined above.

Signed _____(witness) Date _____

Name of Witness (print) _____

Appendix 3: Verbal Consent Form

Patient Information Sheet

"Quality of life following laparoscopic cholecystectomy"

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

You have been asked to take part in this study because you are about to undergo a keyhole operation to have your gallbladder removed. The purpose of this study is to measure how well your symptoms improve after the operation. This will be done by asking you a series of questionnaires relating to your illness. The answers to the questions will be given a score enabling us to quantify your "Quality of Life".

You will be asked to complete the questionnaire before your surgery and repeat the same questionnaire at 6 weeks, 3 months and 2 years after your operation. The questionnaire consists of 36 short questions relating aspects of your illness, how you are feeling, what symptoms you are experiencing and how it impacts on your daily life. The questionnaire takes on average 10 minutes to complete. You are given 5 possible answers to each question, and asked to indicate the most appropriate response.

You will ***not*** be asked to give blood or take part in any other investigation as part of this study, but they may be needed as part of your normal ward treatment.

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

Thank you for taking the time to read this information. If you are kind enough to agree to take part in this study, I would like to remind you that all information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

Please note that the research ethics committee is auditing patient's views of the research process and you may be asked to complete a questionnaire about your experiences.

If you have any further questions do not hesitate to ask, please contact Mr Gareth Kirk in the Department of Surgery, Queen's University of Belfast (phone 02890 240503 ext 2660)

Appendix 4: Patient information sheet

Laparoscopic Cholecystectomy QOL Pro-Forma

Demographic Data

Name

Unit Number

D.O.B.

Interview Date ☐ Tel _____

Consultant ☐

Interviewing Doctor ☐

Referral Type ☐

GP / A&E / Inpatient / Other

Pain / Misc symptoms

Length of Symptoms *(months)* ☐ Pain >3 months *(within the last year)* ☐Y ☐N Nausea ☐Y ☐N Vomiting ☐Y ☐N

Main Site of Pain ☐RUQ ☐Upper (Midline) ☐Other *Specify* _____

Radiation of Pain ☐Back ☐Shoulder Tip ☐Other *Specify* _____

Currently on Rx ☐Y ☐N *Brief details* _____

eg Buscopan , Colofac , Losec , Paracodol etc ..

Cholelithiasis

Proven Gallstones ☐Y ☐N Previous Abnormal LFT's ☐Y ☐N FHx of Gallstones (1st/2nd Degree) ☐Y ☐N

Fat Intolerance ☐Y ☐N Previous Complication ☐Y ☐N

Specify _____

eg Jaundice , Pancreatitis , Cholecystitis etc ..

IBS

Previous Dx ☐Y ☐N FHx of IBS (1st/2nd Degree) ☐Y ☐N Actual Abdominal Distention ☐Y ☐N

Pain Relieved by Defecation ☐Y ☐N More frequent stools with onset of pain ☐Y ☐N Looser stools with onset of pain ☐Y ☐N

Altered Consistency *(Loose or Hard)* ☐Y ☐N Mucous ☐Y ☐N Abnormal Defecation ☐Y ☐N

Specify _____

eg Incomplete evacuation , Straining etc ..

Functional Dyspepsia (Gastroduodenal Disorder)

Organic disease excluded *(Via OGD +/- Ba Meal)* ☐Y ☐N Early Satiety *(Overfull quickly)* ☐Y ☐N Fullness ☐Y ☐N *(Unpleasant sensation like food in the stomach with or without eating)*

Bloating *(Tightness with NO visible swelling)* ☐Y ☐N Previous eradication therapy ☐Y ☐N Relief with eradication ☐Y ☐N

Troublesome Belching ☐Y ☐N Significant Heartburn ☐Y ☐N Dysphagia ☐Y ☐N

Laparoscopic Cholecystectomy QOL Pro-Forma

Psychiatric History

Psychiatric History ☐ Y ☐ N Psychotropic Rx ☐ Y ☐ N Brief Details _____

Quality of Life Questionnaire Completed	Pre-Op	6 weeks Post-Op	3 months Post-Op	2 years Post-Op
	☐ YES	☐ YES	☐ YES	☐ YES

Comments or Other Information

_____

_____

_____

_____

Appendix 5: Patient demographics and symptom details